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No. _____

IN THE

Supreme Court of the United States

APOTEX, INC., APOTEX CORP., and NOVEX PHARMA,
Petitioners,

v.

SYNTEX (U.S.A.) LLC and ALLERGAN, INC.,
Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

PETITION FOR WRIT OF CERTIORARI

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July 9, 2007

QUESTION PRESENTED FOR REVIEW

Before this Court's April 30, 2007 decision in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), the Court of Appeals for the Federal Circuit ("Federal Circuit") affirmed, without an opinion, the district court's rigid and narrow application of the "teaching-suggestion-motivation" ("TSM") test for obviousness, as it existed pre-*KSR*, to find United States Patent No. 5,110, 493 ("the '493 patent") not invalid for obviousness. Specifically, the district court found that the prior art references fail to "suggest, teach, or motivate... whether examined in isolation or collectively" the combination of the pharmaceutical elements claimed in the '493 patent. In *KSR*, the Court rejected this "rigid" and "narrow" application of the TSM test for determining obviousness and, adopted an "expansive and flexible approach" to the obviousness inquiry. In particular, this Court stated in *KSR* that the Federal Circuit erred in concluding that a patent claim cannot be proved obvious merely by showing that the combination of elements was obvious to try. The district court's rigid and narrow obviousness analysis, which rejected the obvious to try defense, is inconsistent with the expansive and flexible approach to obviousness set forth in *KSR*. Accordingly, the question presented for review is:

Whether the Court should grant the writ of certiorari, vacate the judgment below and remand this case to the Federal Circuit (a "GVR Order") for further consideration in light of the intervening *KSR* decision, which changed the application of the obviousness inquiry?

STATEMENT PURSUANT TO RULE 29.6

Petitioners Apotex, Inc., Apotex Corp., and Novex Pharma (which no longer exists) have no parent companies or publicly held companies that own 10% or more of their stock.

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Apotex, Inc., Apotex Corp. and Novex Pharma (collectively "Apotex") respectfully pray that the Court grant this petition for a writ of certiorari to review the Judgment of the United States Court of Appeals for the Federal Circuit ("Federal Circuit") affirming the trial court's decision in this case. Specifically, the decision held United States Patent No. 5,110,493 ("the '493 patent") valid and infringed even though the '493 patent covered an ophthalmic formulation that was virtually identical to the ophthalmic formulation that Syntex (U.S.A) LLC had patented earlier but which differed only by the substitution of one water-soluble, micelle-forming, nonionic surfactant, called Octoxynol 40 ("O_{40}"), for another equivalent one called Polysorbate 80.

OPINIONS BELOW

On December 29, 2003, the United States District Court for the Northern District of California ("district court") issued an opinion which is unreported. (App. 107a-195a).[1] On May 18, 2005, the panel of the Federal Circuit issued an opinion which is reported at *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371 (Fed. Cir. 2005). (App. 69a-103a). In that opinion, the Federal Circuit affirmed the district court's finding of no inequitable conduct and its claim interpretation, and reversed the finding of non-obviousness and identified five critical areas where the district court committed "clear error" in evaluating obviousness and that needed to be considered on remand. (App. 84a-96a). On May 31, 2005, Apotex timely filed a Petition for Panel Rehearing re Inequitable Conduct. On June 13, 2005, the panel of the Federal Circuit denied Apotex' Petition for Panel Rehearing, which is unreported. (App. 104a-106a).

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[1] Reference to "App. #a" is to the Appendix found at the end of this Petition. Reference to "JA #" is to the Joint Appendix filed with the Federal Circuit (Appeal No. 2006-1495) in the second appeal.

On June 2, 2006, the district court issued its opinion on remand, which is unreported. (App. 5a-68a). On April 9, 2007, the panel of the Federal Circuit affirmed, without an opinion, the district court's decision. The Federal Circuit's affirmance is unreported. (App. 1a-2a).

This Court's decision in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007) came down the same day that the mandate in this case was issued by the Federal Circuit on April 30, 2007. Therefore, Apotex could not have timely moved for a rehearing before the Federal Circuit issued the mandate. Accordingly, Apotex moved to (1) recall and stay the mandate and (2) extend the time to request a rehearing. Apotex also filed a Combined Petition for Panel Rehearing and Rehearing *En Banc,* in the event that its Motion for an Extension of Time was granted. On June 5, 2007, the panel for the Federal Circuit denied (1) Apotex' Motion to Recall and Stay the Mandate and (2) its Motion for an Extension of Time to File Combined Petition for Panel Rehearing and Rehearing *En Banc*. The Federal Circuit's June 5, 2007 Order is unreported. (App. 3a-4a). Because Apotex' Motions were denied, its Combined Petition for Panel Rehearing and Rehearing *En Banc* became moot.

The Federal Circuit's April 9, 2007 Judgment (App. 1a-2a) affirming the district court's June 2, 2006 decision on remand (App. 5a-68a) is the subject of this Petition.

STATEMENT OF JURISDICTION

Jurisdiction in the district court was based upon 28 U.S.C. § 1338(a). Jurisdiction in the Federal Circuit was based upon 28 U.S.C. § 1295. On April 9, 2007, the Federal Circuit affirmed the district court's decision. On June 5, 2007 the Federal Circuit denied Apotex' (1) Motion to Recall and Stay the Mandate and (2) Motion for an Extension of Time to File Combined Petition for Panel

Rehearing and Rehearing *En Banc*. This Court has jurisdiction under 28 U.S.C. § 1254(1).

STATUTORY PROVISION INVOLVED

This case concerns the standard of patentability set forth in Section 103(a) of the Patent Act, Title 35, United States Code, which provides:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

STATEMENT OF THE CASE

This Petition is based on the Court's recent decision concerning obviousness in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007).

Syntex (U.S.A.) LLC ("Syntex")[2] owns U.S. Patent No. 5,110,493 ("the '493 patent"; App. 196a-224a) and exclusively licenses Allergan, Inc. ("Allergan") to market the '493 ophthalmic formulation (eye drops) under the mark Acular®. *Syntex*, 407 F.3d at 1373; (App. 71a). On June 6,

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[2] Syntex is now known as Roche Palo Alto.

2001, Syntex and Allergan sued Apotex for technical infringement of the '493 patent based on Apotex filing an Abbreviated New Drug Application ("ANDA") seeking approval to market a generic form of Acular®. *Id.* at 1376; (App. 78a). Apotex denied infringement and alleged that that the '493 patent was invalid and unenforceable. *Id.*; (App. 78a).

The '493 patent is a combination patent that teaches combining a non-steroidal anti-inflammatory drug ("NSAID") such as keterolac tromethamine ("KT") and a quaternary ammonium preservative ("preservative") such as benzalkonium chloride ("BAC") with a nonionic surfactant such as O_{40}. *Id.* at 1373; (App. 71a-72a, 204a). The '493 patent alleges that "a complex was found to form between the NSAID and BAC" making the formulation unstable (*e.g.*, appear cloudy). *Id.* at 1374; (App. 72a, 200a). The '493 patent claims to have solved this problem by adding O_{40} to "stabilize" the formulation. *Id.*; (App. 72a, 202a). This alleged "stabilizing" function of O_{40} made the '493 formulation allegedly novel from the prior art, including Syntex' prior Waterbury patent.

Syntex previously patented the active ingredient in Acular®, KT, and its use in ophthalmic formulations in the Waterbury (JA2348-2361) and Muchowski (JA2314-2332) patents, both of which are now expired. Syntex' prior Waterbury patent teaches ophthalmic formulations containing NSAIDS (such as KT), preservatives (such as BAC) and nonionic surfactants (such as Polysorbate 80) to ***stabilize*** the formulation. (JA2355). Both the surfactant O_{40} of the '493 patent and the Polysorbate 80 of the Waterbury patent belong to the same general class of nonionic

surfactants that are water-soluble and micelle[3]-forming. In an attempt to improperly extend the life of its monopoly over KT formulations, Syntex' '493 patent claims the same ophthalmic formulation as in the expired Waterbury patent but with a different nonionic surfactant – that is substituting O_{40} for Polysorbate 80 in the prior Waterbury patent.

The alleged novelty of using O_{40} in pharmaceutical products is diminished by the Federal Circuit's finding in the first appeal that the use of O_{40} in pharmaceuticals was known at the time of the alleged '493 invention. *Syntex,* 407 F.3d at 1379; (App. 86a; JA2399). The Federal Circuit found this to be "an important fact to consider in assessing the obviousness of the claims in suit" and it is the law of the case. *Id.*; (App. 86a); *see also State Indus., Inc. v. Mor-Flo Indus., Inc.*, 948 F.2d 1573, 1576 (Fed. Cir. 1991) (under the law of the case doctrine, "findings of fact reviewed in and relied upon in an appellate court's decision become law of the case and, absent certain exceptional circumstances, may not be disturbed by a trial court on remand") (internal citations omitted). The '493 inventors made this admission in a report that Syntex submitted to the FDA at the time that Syntex had filed the application for the '493 patent. (JA2395-2425).

A. The relevant prosecution history.

The '493 patent issued from ASN 07/624,027 ("Second Application") filed December 7, 1990, a continuation of ASN 07/096,173 ("First Application") filed September 11, 1987. *Syntex*, 407 F.3d at 1374; (App. 73a). The Examiner only allowed the '493 patent because the

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[3] A micelle is a molecular cage of different shapes and sizes, having a hydrophilic ("water loving") exterior and a hydrophobic ("water hating") interior. A hydrophobic drug can be captured within the micelle and be solubilized by the hydrophobic exterior of the micelle.

"Lidgate Declaration" and the corresponding amendment made it appear that O_{40} produced "unexpected results" over other nonionic surfactants. (JA3757).

1. The Examiners repeatedly rejected the '493 claims as obvious over the prior art.

Every Examiner[4] who reviewed the '493 application rejected the claims as obvious over the prior art without a showing of "unexpected results" from using O_{40}. (JA3482-3484; JA3736-3738). The Examiners stated that Gilbert (JA2333-2341) and Han (JA2362-2365) teach ophthalmic compositions using the claimed NSAID (KT), a preservative (BAC) and "that it is known to use nonionic surfactants as stabilizing agents in ophthalmic compositions containing NSAID." *Syntex*, 407 F.3d at 1375, 1382; (App. 74a, 92a; JA3482-3483, JA3736-3737). Gilbert, like Waterbury, taught Polysorbate 80 as a stabilizer. *Syntex*, 407 F.3d at 1374; (App. 74a).

The Examiners also found that the only ingredient lacking in Gilbert and Han was O_{40}, and that O_{40} was found in *McCutcheon's* (JA2371-2372), which lists Igepal CA-897 (the trade name for O_{40}) as a known emulsifier and stabilizer. *Syntex*, 407 F.3d at 1374-75; (App. 74a). In particular, the Examiners stated: "The mere substitution of one nonionic for another, that is, the nonionic of McCutcheon's [O_{40}] for the nonionic of the primary reference is not deemed a patentable distinction in the absence of a showing of some unobvious result." (JA3482; JA3736); *see also Syntex*, 407 F.3d at 1375; (App. 74a-75a).

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[4] Different Examiners at the PTO examined the Applications, but they all rejected the claims for obviousness on virtually identical grounds. (JA3482-3484; 3736-3738).

2. After Syntex submitted the Lidgate Declaration purporting to show O_{40}'s "unexpected results," the Examiner allowed the '493 claims.

To overcome the obviousness rejection in the Second Application, Syntex submitted the Lidgate Declaration (JA3746-3748) purporting to show that O_{40} produced "unexpected results."[5] *Syntex*, 407 F.3d at 1375; (App. 75a). The Lidgate Declaration compared ophthalmic compositions containing KT, BAC and one of the nonionic surfactants O_3, O_5 (both water ***in***soluble) and O_{40} (water soluble)[6] and claimed that O_{40} in the ophthalmic compositions produced a clear solution while the other two did not. (JA3747). Based on the Lidgate Declaration, Syntex argued that O_{40} produced "unexpected results." (JA3751). Syntex failed to include in this Declaration Lidgate's results of a KT/BAC composition containing $O_{12.5}$ which showed that $O_{12.5}$ (which, like O_{40}, is water-soluble) acted the same as O_{40}, and that O_{40}, therefore, did not produce "unexpected results" in the composition. *See Syntex*, 407 F.3d at 1375; (App. 75a; JA2686, JA2711).

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[5] During the examination of the First Application, the Examiner rejected the "Unverified Data" submitted by Syntex that purported to show that O_{40} outperformed the surfactants polysorbate 80 (tween 80) and myrj 52 because the "Unverified Data" lacked scientific integrity and was flawed. *Syntex*, 407 F.3d at 1382; (App. 92a-93a; JA3501). The first Examiner's reasons for rejecting the Unverified Data included the fact that O_{40} was not compared to the surfactants of the primary references, the concentration of O_{40} was greater than that of the other surfactants and the data was not submitted in Declaration form under oath. *Id.*; (App. 92a-92a; JA3501). Dr. Mitra's testimony (Apotex' expert) confirmed the flaws in the Unverified Data. (JA1321-1323; JA1414-1419; JA1492-1493, JA1593).

[6] The subscript numerals "3," "5," and "40" refer to the respective "alkyl chain" lengths (also referred to as "ethylene oxide" units) of the Octoxynols.

The Examiner, who did not know about the missing $O_{12.5}$ test results, made it clear in his reasons for allowance that he was allowing the claims of the '493 application based solely on the alleged unexpected results from using O_{40} that Syntex claimed in the Lidgate Declaration:

> Applicant has overcome the prior rejections made under 35 U.S.C. 103 by showing that **unexpected results are obtained when one uses the surfactant of the instant invention [O_{40}].** These results are unobvious because one of ordinary skill in the art would not have known that one surfactant would outperform other surfactants. (Emphasis added).

Id. at 1375; (App. 75a; JA3757).

B. The proceedings below.

In June 2003, the district court held a bench trial on the issue of validity. On December 29, 2003, the district court issued its Findings of Fact and Conclusions of Law (App. 107a-195a) and found the '493 patent enforceable and not invalid. (App. 195a). Apotex appealed, among other things, the district court's determination of non-obviousness to the Federal Circuit.

On May 18, 2005, the Federal Circuit reversed the district court's ruling on non-obviousness. *Syntex*, 407 F.3d at 1385; (App. 99a). The Federal Circuit found clear error regarding several of the factual findings underlying obviousness and the misapplication of certain legal presumptions, and remanded this issue for reconsideration with the following guidelines that are relevant to this Petition:

First, the Federal Circuit found that the record "reflects that the use of O_{40} in pharmaceutical compositions was known in the art at the relevant time, an important fact to consider in assessing the obviousness of the claims." *Syntex*, 407 F.3d at 1379; (App. 86a).

Second, the Federal Circuit found that, contrary to Respondents' assertions at trial, the cited prior art references *do not teach away* from the use of O_{40} as a nonionic surfactant in ophthalmic formulations involving NSAIDs and BAC, but rather "*provide material disclosure.*" *Id.* at 1380; (App. 87a-88a).

Third, the Federal Circuit held that the testimony of Apotex' expert, Dr. Mitra, must be reconsidered as to whether one skilled in the art would be motivated to combine the prior art references and whether O_{40} truly produced "unexpected results" to someone of that skill level. *Id.* at 1381-82; (App. 89a-91a).

Fourth, the Federal Circuit expressed concern with Syntex' contradictory statements and its failure to disclose pertinent data (the $O_{12.5}$ results) to the United States Patent and Trademark Office ("PTO") while prosecuting the '493 patent. Specifically, the Federal Circuit questioned whether O_{40} produced "unexpected results" sufficient to justify patentability in light of the undisclosed $O_{12.5}$ test results. *Id.* at 1383; (App. 94a-95a).

On remand, the district court found the '493 patent non-obvious (App. 67a) and did not follow the Federal Circuit's explicit instructions for reevaluating the factual findings underlying the obviousness inquiry. Nonetheless, the Federal Circuit affirmed (App. 1a-2a), without an opinion, the district court's decision after remand.

First, the district court did not acknowledge and gave little or no weight to the Federal Circuit's explicit finding that the use of O_{40} in pharmaceuticals was well-known in the art when the application for the '493 patent was filed. Second, the district court did not follow the Federal Circuit's instructions that the prior art references provide *material disclosure* of the prior use of O_{40} in related products and, instead, tried to distinguish the prior art as it did before. Third, the district court failed to address the Federal Circuit's instruction to reconsider Apotex' expert testimony on whether O_{40} produced unexpected results. Instead, the district court analyzed whether Apotex' expert accurately compared the O_{40} test results with the test results of other surfactants. Fourth, the district court did not follow the Federal Circuit's instructions to reconsider the omission of the $O_{12.5}$ test results from the prosecution history and whether it was established that O_{40} did, in fact, produce unexpected results.

The difference between the '493 ophthalmic formulations and the ophthalmic formulations in the prior Waterbury, Gilbert and Han patents is the particular type of water-soluble, micelle-forming nonionic surfactant used. Thus, the issue becomes whether a person of ordinary skill in the art ("POSA") would have been motivated to substitute the equivalent O_{40} for the surfactants listed in these prior art patents since O_{40} was known for use in pharmaceuticals per Syntex' report. Had the district court applied an "expansive and flexible" approach to the obviousness inquiry as set forth in *KSR*, it would have found that according to a POSA, simply substituting one well-known water-soluble, micelle-forming nonionic surfactant for another in a pharmaceutical composition is obvious. This is especially true in light of the withheld $O_{12.5}$ test results which showed that O_{40} did not produce unexpected results.

REASONS FOR GRANTING THE WRIT

A. The Judgment of the Federal Circuit should be reversed because it conflicts with the "expansive and flexible approach" to obviousness that was set forth by this Court in *KSR*.

This case warrants a grant of writ because the Federal Circuit's decision was rendered prior to, and conflicts with, the Court's decision in *KSR*. In *KSR*, this Court rejected the Federal Circuit's use of a narrow, rigid application of the "teaching, suggestion, or motivation (TSM) test," but instead should use an "expansive and flexible approach." *KSR*, 127 S. Ct. at 1730-31, 1739, 1746.

In *KSR*, the Engelgau patent (the patent-in-suit) covered a vehicle accelerator pedal whose position could be moved to adjust for the height of the driver. The pedal included an electronic sensor on a fixed support to control the engine. *Id.* at 1736-37. The Asano prior art patent disclosed every feature of the patented invention except for the use of an electronic sensor to detect the position of the pedal and transmit it to the computer controlling the engine. The Smith prior art patent disclosed the use of electronic sensors to control engines. *Id.* at 1735-37.

The district court found the Engelgau patent invalid because it was an obvious combination of the prior art. *Id.* at 1737-38. The Federal Circuit reversed, finding that the district court did not apply the "teaching, suggestion or motivation" test strictly enough because the district court:

> failed to make "'findings as to the specific understanding or principle within the knowledge of a skilled artisan that would have motivated one with no knowledge of [the] invention' ... to attach an electronic

> control to the support bracket of the Asano assembly."

Id. at 1738 (citations omitted).

This Court reversed and rejected the Federal Circuit's "rigid approach" to the question of obviousness, stating that "our cases have set forth an expansive and flexible approach inconsistent with the way the Court of Appeals applied its TSM test here." *Id.* at 1739.

This Court cautioned that the TSM test could not be applied as a "rigid and mandatory formula" or a "rigid rule that limits the obviousness inquiry." *Id.* at 1741. Specifically, "[t]he obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation..." and that "a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* This Court made clear that it was not appropriate to apply "[r]igid preventative rules that deny factfinders recourse to common sense... ." *Id.* at 1742-43 (citations omitted).

This Court also explained that "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 1742. Moreover, in certain circumstances a patented invention would have been obvious if it would have been "obvious to try." *Id.*

Applying an expansive and flexible approach to the obviousness inquiry, this Court held that the patented invention was an obvious combination of the height-adjustable pedal and electronic sensors in the prior art. *Id.* at 1743-45.

1. The district court's rigid and formalistic application of the TSM test is inconsistent with the expansive and flexible approach to obviousness under *KSR*.

The district court incorrectly required that "[t]he showing of a suggestion, teaching or motivation to combine references 'must be clear and particular'." (App. 49a at ¶ 97) citing *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999). Such an approach to the TSM analysis was unduly rigid and formalistic and is inconsistent with the expansive and flexible to the obviousness inquiry under *KSR*. 127 S. Ct. at 1739-43.

The district court's finding of a lack of motivation to combine the prior art references to arrive at the '493 formulations was based primarily on three reasons, which are severely undermined in view of the *KSR* decision, as explained below.

First, the district court made a rigid finding that the prior art references do not teach, suggest or motivate the use of O_{40} in *ophthalmic formulations*, as follows:

> Moreover, the Court finds that there is no evidence that O_{40} was used in an ophthalmic product or formulation before the inventions of the '493 patent.

(App. 29a at ¶ 49).

> [T]he record fails to establish by clear and convincing evidence that any of the references suggest, teach, or motivate use of O_{40} in an ophthalmic formulation. Particularly, Waterbury expressly teaches the use of Polysorbate 80. Han, in

> comparison, teaches the use of nonionic surfactants, generally. Gilbert discloses ophthalmic formulations that may contain a stabilizer, only some of which are nonionic surfactants. Thus, the references relied upon by Defendants, whether examined in isolation or collectively, would not have suggested a motivation to combine to one skilled in the art at the time of the patent application.

(App. 34a-35a at ¶ 62).

Second, the district court made a rigid finding that the prior art references do not discuss the *problem* allegedly solved by the '493 patent, namely the use of O_{40}, or other surfactants in that same class, to stabilize any KT/BAC interaction or complex, as follows:

> [Syntex' own prior] Waterbury patent does not discuss any problem of interaction or complexation between BAC and ketorolac tromethamine [KT], and does not include Polysorbate 80 in an example formulation, and therefore does not show 'that the non-ionic surfactant Polysorbate 80 solubilizes BAC.'

(App. 36a-37a at ¶ 67).

> Moreover, because *McCutcheon's* discloses the use of O_{40} only in the context of mixing non-water-miscible materials with water, *McCutcheon's* fails to provide any expectation that O_{40} could be successfully used to stabilize solutions that do not contain an oil-based component. There is

> nothing in *McCutcheon's* that provides any expectation that O_{40} could successfully stabilize the interaction of an NSAID and a preservative or that O_{40} could safely be used in an ophthalmic formulation.

(App. 56a at ¶ 111).

Third, the district court made a rigid finding that the prior art references do not suggest substituting surfactants or the equivalency of O_{40} to other surfactants, as follows:

> None of the prior art references cited by Defendants disclose any functional equivalence between O_{40} and any of the surfactants disclosed by the Waterbury, Gilbert or Han patents.

(App. 18a at ¶ 19).

> Nor is there any motivation to modify the teachings of the Waterbury, Gilbert or Han patents to substitute O_{40} for the surfactants disclosed in those references. There is nothing in these patents that suggests that one should search for a substitute surfactant, or that discloses a functional equivalency between O_{40} and other water-soluble, micelle-forming, non-ionic surfactants - or among all surfactants possessing these properties.
>
> Because Defendants have pointed to no expectations of - or prior art references disclosing - functional equivalency between O_{40} and any surfactant disclosed in the Waterbury, Gilbert or Han patents,

> Defendants' focus on the substitutability of O_{40} for these prior art surfactants remains an improper use of hindsight.

(App. 56a, 58a at ¶¶ 112-113).

This lack of motivation finding is illustrative of the unduly rigid and formalistic manner in which the district court applied the TSM test in violation of *KSR*. In particular, this Court in *KSR* stated that the motivation to combine may be found in "design incentives and other market forces ... either in the same field [as the patented invention] or a different one." *KSR*, 127 S. Ct. at 1740. Since motivation may be found in *a different field altogether* from the patented product, it is of no consequence that the district court found that O_{40} was not previously used in ophthalmics.

Even if O_{40} was not previously used in ophthalmics, O_{40} was a well-known ingredient in pharmaceutical products, as the '493 inventors admitted in the Syntex report. In addition, Apotex' expert, Dr. Mitra, testified that "O_{40} was very well known in [the] cosmetic industry and has been used in many products." (App. 35a at ¶ 63). The use of O_{40} in cosmetics and in the '493 ophthalmic formulations are topical uses of O_{40}. Such prior uses of O_{40} provide the requisite motivation to combine the prior art under *KSR* to arrive at the '493 formulations.

It is of no consequence that O_{40} was not mentioned in the prior art patents because *KSR* rejected such a formalistic approach and a motivation to combine need not be explicitly identified in the asserted references, as this Court explained:

> The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the

> importance of published articles and the explicit content of issued patents. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way. In many fields it may be that there is little discussion of obvious techniques or combinations, and it often may be the case that market demand, rather than scientific literature, will drive design trends.

KSR, 127 S. Ct. at 1741. Rather, courts are to view the TSM test *from the perspective of a POSA*, who possesses knowledge beyond that disclosed within the four corners of the asserted references. *See id.* (The motivation inquiry for obviousness "need not seek out precise teachings directed to specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.").

It is also irrelevant that the prior art did not mention the alleged *problem* solved by the '493 patent because *KSR* rejected the assumption "that a person of ordinary skill attempting to solve a problem will be led only to those elements of prior art designed to solve the same problem." *Id.* at 1742. This Court explained that "[c]ommon sense teaches, however, that familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* *KSR* also explained that "[u]nder the correct analysis, any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.*

Further, this Court in *KSR* articulated a multitude of sources from which a motivation to combine may be found,

including, "look[ing] to interrelated teaching of multiple patents; to the effects of demands known to the design community or present in the market place and the background knowledge possessed by a person having ordinary skill in the art." *Id.* at 1740.

In the first appeal, the Federal Circuit found that Apotex' expert, Dr. Mitra, provided his opinion of why a POSA would have been motivated to use O_{40} in the claimed formulation. *Syntex*, 407 F.3d at 1381; (App. 89a-91a). As the Federal Circuit noted, Dr. Mitra explained that Waterbury and Gilbert show that water-soluble, micelle-forming nonionic surfactants, such as Polysorbate 80, solubilize the NSAID/preservative (*e.g.*, KT/BAC) formulation (JA1527-1528; JA2207-2208) and; therefore, a POSA reading these references "would expect that other nonionic surfactants would work equally well and one would thus look to other patents/publications which show that other nonionic surfactants such as O_{40} function as a surfactant." *Syntex*, 407 F.3d at 1381, n. 10; (App. at 90a, n. 10). In fact during the prosecution, the PTO rejected what became claim 1 of the '493 patent over *McCutcheon's*, because substituting O_{40} for the other surfactants disclosed in Gilbert and Han was not a patentable distinction. (JA3482; JA3736).

A POSA would have known to use O_{40} because the use of O_{40} in pharmaceuticals was well-known at the time of the alleged '493 invention (*see* admission in the Syntex report at JA2399) and, as stated by the Federal Circuit, this was "an important fact to consider in assessing the obviousness of the claims in suit." *Syntex*, 407 F.3d at 1379; (App. 86a). Also, *McCutcheon's* teaches that O_{40} "was a known stabilizer" and *McCutcheon's* "cannot be so lightly overlooked." *Id.* at 1380; (App. 88a).

The Federal Circuit further noted that "Dr. Mitra also opined that knowledge of the chemical qualities of

surfactants useful to the claimed subject matter would cause a person, 'as a matter of science' to 'go into another nonionic surfactant like octoxynols.'" *Id.* at 1381-82; (App. 91a). "Structural relationships often provide the requisite motivation to modify known compounds to obtain new compounds." *In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997), *citing In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995).

Both octoxynols and polysorbates have "close structural and chemical similarity" because they use ethylene oxide units to form their chemical chain. (JA1550-1551). Here, a POSA would infer, from the "close structural and chemical similarity" of O_{40} to Polysorbate 80, that both compounds were "capable of solubilizing the KT/BAC complex by encapsulation." *Syntex*, 407 F.3d at 1381 n. 11; (App. 91a, n. 11). That is, because Polysorbate 80 was capable of solubilizing the KT/BAC complex, it would be "predictable" to a POSA that another structurally and chemically similar nonionic surfactant, like O_{40}, would also solubilize the KT/BAC complex. *See KSR*, 127 S. Ct. at 1740 ("If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.").

Regardless of whether O_{40} was previously used in ophthalmics, *KSR* dictates that a POSA would use "common sense" in using the "familiar item" O_{40} in place of the structurally and chemically similar Polysorbate 80 as a surfactant in an ophthalmic formulation. *See id.* at 1742-43 ("Rigid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it."); *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1161 (Fed. Cir. 2007) ("[T]he common sense of those skilled in the art demonstrates why some combinations would have been obvious where others were not.") (citing *KSR*).

Due to their structural similarity, it would have been "predictable" to a POSA to substitute O_{40} for Polysorbate 80 in the prior KT/BAC formulations making the '493 patent obvious under *KSR*. 127 S. Ct. at 1739 ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."). The use of O_{40} in the '493 formulations is nothing more than "the mere substitution of one element for another known in the field" and yields a "predictable result" making the '493 patent obvious. *See id.* at 1740.

In *KSR*, this Court rejected the notion that "obvious to try" is *per se* an improper standard by which to assess obviousness. *Id.* at 1742 Rather, in certain circumstances a patented invention would have been obvious if it would have been "obvious to try:"

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

Id. Since Polysorbate 80 solubilizes any KT/BAC complex and both O_{40} and Polysorbate 80 are structurally similar, a POSA would have found it "obvious to try" O_{40} to solubilize any KT/BAC complex. The "obvious to try" test articulated in *KSR* further demonstrates the error the district court committed by rigidly applying the TSM test and defying

common sense to find no motivation to combine the prior art references to arrive at the formulations of the '493 patent.

The Federal Circuit's reevaluation of the record in accordance with the "expansive and flexible" obviousness principles set forth in *KSR* would show that the '493 patent is invalid for obviousness.

2. The alleged unexpected results do not overcome the *prima facie* showing of obviousness under *KSR*.

A *prima facie* showing of obviousness may be rebutted by demonstrating that the patented invention achieved unexpected results, *i.e.*, "some superior property or advantage that a [POSA] would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

In its May 18, 2005 Order, the Federal Circuit found that "this case is unusual because certain key facts existed that give rise to some doubt as to the strength of the factual proposition that O_{40} indeed produced unexpected results." *Syntex*, 407 F.3d at 1383; (App. 94a-95a). *See also id.* at 1379; (App. 85a) ("[W]e think the district court failed to appreciate that the prosecution history of the relevant patents ... casts some doubt on the final examiner's conclusion that the claimed surfactant [O_{40}] produces unexpected results sufficient to overcome a prima facie case of obviousness."). The Federal Circuit questioned the veracity of the Lidgate Declaration due to the omitted data showing that $O_{12.5}$ performed comparable to O_{40}. In fact, the Federal Circuit found the withheld $O_{12.5}$ test results "material to Lidgate's statement that O_{40} was generally superior to other octoxynols in stabilizing the KT/BAC formulation." *Id.* at 1384; (App. 98a).

Where, as here, the allegedly "unexpected results" are highly questionable, they cannot rebut the *prima facie* showing of obviousness in view of *KSR*. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007) ("[W]e hold that even if Pfizer showed ... unexpectedly superior results, this secondary consideration does not overcome the strong showing of obviousness in this case."); *Leapfrog*, 485 F.3d at 1162 ("given the strength of the prima facie obviousness showing, the evidence on secondary considerations was inadequate to overcome a final conclusion that claim 25 would have been obvious").

Despite the Federal Circuit's skepticism regarding Syntex' claim of unexpected results and its instructions on remand for reevaluating unexpected results, the district court nonetheless found that Syntex had demonstrated unexpected results. This error is partially based on the district court's reliance on patentee Lidgate's belief that sufficient tests were not performed to confirm that $O_{12.5}$ and O_{40} were equivalent in the KT/BAC formulations. (App. 26a-27a, 31a, 51a-52a at ¶¶ 40, 41, 54 and 104). Such reliance on the patentee's, and not a POSA's, knowledge is inconsistent with *KSR*. *See* 127 S. Ct. at 1741-42 ("[N]either the particular motivation nor the avowed purpose of the patentee controls."..."The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art.").

The alleged uniqueness of O_{40} in the '493 patent is diminished by the admissions that Syntex made in the '493 patent and its file history. For example, in the First Application where Syntex claimed "a stabilizing amount of a nonionic surfactant" (JA3448), not just O_{40}, Syntex admitted that other water-soluble, nonionic surfactants were equivalent to O_{40} in the '493 formulations. Similarly, in the '493 patent (App. 207a), Syntex listed several nonionic

surfactants that are purportedly useful in the '493 formulations:

> The nonionic surfactants useful in the formulations of the present invention are preferably polyoxyethylated surfactants including polyoxyethylene hydrogenated vegetable oils, such as polyethylene 60 hydrogenated castor oil, manufactured and sold by Kao Corp. of Japan under the trade name Emanon CH-60, and preferably ethoxylated octylphenol compounds, such as **Octoxynol 10**[7] and most preferably Octoxynol 40, manufactured and sold by GAF under the trade name Igepal CA897 (a 70% aqueous solution of Octoxynol 40). (App. 27a) (Emphasis added).

In sum, the evidence of alleged unexpected results needs to be reevaluated using the "expansive and flexible" approach to the obviousness inquiry, as set forth in *KSR*, which would show that O_{40} did not produce unexpected results.

B. This case satisfies the requirements for a grant of certiorari, vacation of the judgment and remand to the Federal Circuit.

This Court grants certiorari, vacates a judgment, and remands ("GVR") when it concludes that intervening precedent is "sufficiently analogous and, perhaps, decisive to compel re-examination of the case." *Henry v. City of Rock*

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[7] Syntex thus admitted that any octoxynol of O_{10} and greater would work in the alleged invention; thus O_{40} did not produce unexpected results.

Hill, 376 U.S. 776, 777 (1964). This Court has explained that:

> Where intervening developments, or recent developments that we have reason to believe the court below did not fully consider, reveal a reasonable probability that the decision below rests upon a premise that the lower court would reject if given the opportunity for further consideration, and where it appears that such a redetermination may determine the ultimate outcome of the litigation, a GVR order is, we believe, potentially appropriate.

Lawrence v. Chater, 516 U.S. 163, 167 (1996) (per curiam). Further, "[w]hether a GVR order is ultimately appropriate depends further on the equities of the case," including whether "the delay and further cost entailed in a remand are not justified by the potential benefits of further consideration by the lower court." *Id.* at 167-68.

"[A] GVR order both promotes fairness and respects the dignity of the Court of Appeals by enabling it to consider potentially relevant decisions and arguments that were not previously before it." *Stutson v. United States*, 516 U.S. 193, 197 (1996). This Court has granted GVRs in numerous instances due to monumental intervening decisions of this Court concerning patent law, like *KSR*.[8] This case plainly meets the Court's standard for granting a GVR Order.

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[8] *See, e.g., Medimmune, Inc. v. Centocor, Inc.*, 127 S. Ct. 1118 (2007) (granting GVR order for further consideration in light of this Court's decision regarding standing of a licensee to seek a declaratory judgment of invalidity of the licensor's patent in *Medimmune, Inc. v. Genentech, Inc.*, 127 S. Ct. 764 (2007)); *Intermatic Inc. v. Lamson & Sessions Co.*, (cont'd...)

The relevant intervening *KSR* decision was not considered by the Federal Circuit or the district court and there is more than a "reasonable probability that the decision below rests upon a premise that the lower court would reject if given the opportunity for further consideration." *Lawrence*, 516 U.S. at 167. As explained above, the district court applied a rigid and formalistic TSM test to find that the '493 patent is not obvious. Such a narrow test is inconsistent with the expansive and flexible approach to the obviousness inquiry and the common sense notion set forth in *KSR*. 127 S. Ct. at 1742. If either the Federal Circuit or the district court is given the opportunity to reevaluate the record in light of the intervening *KSR* decision, it is very likely that it will find the '493 patent obvious. "[S]uch a redetermination may re-determine the ultimate outcome of the litigation." *Lawrence*, 516 U.S. at 167.

Finally, "the equities of the case" strongly favor issuing a GVR Order. Any delay caused by another remand for reevaluation of the record would not prejudice Respondents because their monopoly on the sales of Acular® would continue uninterrupted. The additional costs incurred on remand would be negligible compared to the amount of money the parties already expended in this litigation. Respondents would still benefit monetarily from their continued sales of Acular® during a remand. Further,

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537 U.S. 1016 (2002) (granting GVR order for further consideration in light of this Court's decision regarding prosecution history estoppel in *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002)); *Honeywell, Inc. v. Litton Sys., Inc.*, 520 U.S. 1111 (1997) (granting GVR order for further consideration in light of this Court's decision regarding the doctrine of equivalence in *Warner-Jenkinson Co., Inc. v. Hilton Davis Chemical Co.*, 520 U.S. 17 (1997)); *U.S. Surgical Corp. v. Ethicon, Inc.*, 517 U.S. 1164 (1996) (granting GVR order for further consideration in light of this Court's decision regarding construction of patent claims in *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996)).

any delay and costs is more than outweighed by the significant cost savings to consumers through generic Acular® if the '493 patent is found invalid.

CONCLUSION

Apotex respectfully requests that the Court issue a GVR Order for reconsideration of the '493 patent in view of the *KSR* decision, which will likely lead to a finding of obviousness of the '493 patent.

Respectfully submitted,

July 9, 2007

By: /s/

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United States Court of Appeals for the Federal Circuit

[ENTERED: April 9, 2007]

2006-1495

SYNTEX (U.S.A.) LLC, and ALLERGEN, INC.,

Plaintiffs-Appellees,

v.

APOTEX, INC., APOTEX CORP., and NOVEX PHARMA,

Defendants-Appellants.

Judgment

ON APPEAL from the **UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF CALIFORNIA**

In CASE NO(S). **01-CV-2214**

This CAUSE having been heard and considered, it is

ORDERED and ADJUDGED:

Per Curiam (RADER, GAJARSA, and PROST, Circuit Judges).

AFFIRMED. See Fed. Cir. R. 36.

ENTERED BY ORDER OF THE COURT

DATED April 9, 2007

/s/
Jan Horbaly, Clerk

United States Court of Appeals for the Federal Circuit

2006-1495

SYNTEX (U.S.A.) LLC,
and ALLERGAN, INC.,

Plaintiffs-Appellees,

v.

APOTEX, INC., APOTEX CORP.,
and NOVEX PHARMA,

Defendants-Appellants.

ON MOTION

Before RADER, GAJARSA, and PROST, Circuit Judges.

ORDER

Apotex, Inc., et al. move to (1) recall and stat the mandate, and (2) for an extension of time, to file their combined petition for panel rehearing and rehearing en banc. Syntex (U.S.A.) LLC et al., opposes. Apotex replies.

Upon consideration thereof,

IT IS ORDERED THAT:

The motions are denied.

FOR THE COURT

June 5, 2007 /s/

Date Jan Horbaly
Clerk

cc: Robert S. Silver, Esq.
Alexander L. Brainderd, Esq.

IN THE UNITED STATES DISTRICT COURT FOR

THE NORTHERN DISTRICT OF CALIFORNIA

SYNTEX (U.S.A.) LLC, a Delaware corporation; ALLERGAN, INC., a Delaware corporation

Plaintiffs,

v.

APOTX INC., a Canadian corporation; APOTEX CORP., a Delaware corporation; and NOVEX PHARMA, a Canadian corporation.

Defendants.

No. C 01-02214 MJJ

FINDINGS OF FACTS AND CONCLUSIONS OF LAW ON RE-HEARING ON ISSUE OF OBVIOUSNESS OF THE '493 PANTENT AND PLAINTIFFS' REQUEST FOR PRELIMINARY INJUNCTIVE RELEIF

Pending before the Court is Plaintiffs Syntex (U.S.A.) LLC and Allergan, Inc.'s Request for Preliminary Injunctive Relief. Concurrent with Plaintiffs' Request, and pursuant to the Federal Circuit's decision in *Syntex (U.S.A.)LLC v. Apotex, Inc.*, 407 F.3d 1371 (Fed. Cir. 2005), is the Court's re-

hearing on Defendants Apotex Inc., Apotex Corp., and Novex Pharma's (collectively, "Defendants") obviousness challenge to Plaintiffs' patents-in-suit. In accordance with this Court's Order, the parties have filed Opening Briefs (Doc. #469 (Plaintiffs' Corrected Opening Brief "POB"), Doc. #464 (Defendants' Opening Brief "DOB"), and Responsive Briefs (Doc. #470 (Plaintiffs' Responsive Brief "PRB"), Doc. #471 (Defendants' Responsive Brief "DRB"). The Court has carefully considered the parties' arguments as set forth in their briefs and at oral argument, and has thoroughly reviewed and considered the evidentiary record in light of the controlling law and the directives set forth in the Federal Circuit's decision. The Court now rules as follows.

I. Background

Syntex owns U.S. Patent No. 5,110,493 ("the '493 patent"), entitled "Ophthalmic NSAID Formulations Containing a Quaternary Ammonium Preservative and a Non-ionic Surfactant." Allergen is the exclusive distributor and manufacturer of formulations of the '493 patent, including the product ACULAR®, an ophthalmic solution used for treating eye inflammation. On April 25,2001, Defendants notified Plaintiffs pursuant to 21 U.S.C. § 355(j)(2)(B), that they had filed Abbreviated New Drug Application ("ANDA") 76-109 with the Food and Drug Administration, wherein Defendants sought approval to market a generic drug version of ACULAR®. In their notice, Defendants stated that they believed the '493 patent to be invalid on the grounds of obviousness and inequitable conduct, and

not infringed by Defendants' proposed generic version of ACULAR®.

In response, on June 6, 2001, Plaintiffs filed this lawsuit against Defendants for patent infringement under 21 U.S.C. § 355 and 35 U.S.C. § 271(e). Plaintiffs thereafter moved for summary judgment of infringement. The Court granted partial summary judgment for Plaintiffs, finding that the submission of ANDA 76-109 literally infringed each claim of the '493 patent

Pursuant to 21 U.S.C. § 355(j)(5)(B)(iii), approval of ANDA 76-109 was stayed for 30 months from receipt of Defendants' notification of the ANDA filing. The stay was set to expire at the end of October, 2003, and, absent a preliminary injunction from this Court, the FDA was then free to approve ANDA 76-109 while the Court's decision on the issue of the '493 patent's validity was pending. As a result, on October 17, 2003, Plaintiffs filed a Motion for a Temporary Restraining Order and Preliminary Injunction, requesting that the Court enjoin Defendants from engaging in the commercial manufacture, use, or sale of any product, the approval of which is sought through ANDA 76-109, until the Court determined the validity and enforceability of the '493 patent.

In ruling on Plaintiffs' Motion, the Court noted that because Plaintiffs had already prevailed on their infringement claim, to prevail on the merits, Plaintiffs only needed to withstand Defendants' invalidity challenges, which included unenforceability due to obviousness, lack of utility,

lack of enablement, indefiniteness, and inequitable conduct. Based upon its review of the record, the Court held that Plaintiffs had sufficiently established a substantial likelihood that they would prevail on the issues of patent validity, and that the balance of harms weighed in favor of granting injunctive relief. The Court therefore granted the preliminary injunction.

In June 2003, in the interim between the Court's ruling on the Motion for Summary Judgment and its Order granting a preliminary injunction, the Court held a bench trial on Defendants' claims of invalidity and unenforceability of the '493 patent. Subsequently, on December 29, 2003, the Court issued its Findings of Fact and Conclusions of Law ("the December 29 Order"), wherein it concluded that Defendants' proposed generic version of ACULAR® directly infringed all of the claims of the '493 patent and that the '493 patent was not invalid. In particular, the Court rejected Defendants' invalidity arguments based on obviousness. The Court also affirmed the preliminary injunction by permanently enjoining Defendants from selling products described in ANDA 76-109. Defendants thereafter appealed this Court's determination of non-obviousness to the Court of Appeals for the Federal Circuit

On May 18, 2005, the Federal Circuit issued its Order reversing this Court's ruling on non-obviousness and outlining criteria that the Court is to consider on remand. Defendants subsequently moved to vacate the permanent injunction pursuant to Federal Rule of Civil Procedure 60(b)(5). The

Court denied Defendants' request; however, on December 15, 2005, the Federal Circuit vacated the permanent injunction. (Doc. #437.)

Thereafter, on December 16, 2005, Plaintiff filed an Application for a Temporary Restraining Order, seeking to prevent Defendants from commercially manufacturing, using, offering to sell, or selling within the United States or importing into the United States any drug product the approval for which is sought through ANDA 76-109. On December 29, 2005, the Court granted Plaintiffs' Motion for a Temporary Restraining Order (Doc. #447). The parties subsequently stipulated that the Temporary Restraining Order would remain in effect until the Court's hearing on the Plaintiffs' Motion for a Preliminary Injunction and concurrent hearing on the issue of obviousness. (Docs. #463, 473.) On February 23, 2006, the Court held a hearing on Plaintiffs' Motion for Preliminary Injunction and on Defendants' obviousness challenge to the claims of the '493 patent pursuant to the Federal Circuit's remand. The Court now makes the following factual findings and legal conclusions on the issue of obviousness and Plaintiffs' request for injunctive relief.[1]

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[1] As an initial matter, also pending before the Court is Plaintiffs' Motion to Remove from the Record Evidence Inadvertently Placed in the Record at Trial (Doc. #427). In their Motion, Plaintiffs argue that, although the Court only admitted specific pages from Dr. Mitra's expert report during trial, the entire report was placed in the record. (Mot. at 2.) Defendants oppose Plaintiffs' Motion, arguing that granting the Motion would contravene the Federal Circuit's mandate, and that even if the Court only admitted selected pages from the report into evidence, Plaintiffs failed to correct this error. In support of their Motion, Plaintiffs cite the following exchange from trial:

II. Obviousness

A. Findings of Fact

1. Preliminary Factual Findings

1. The '493 patent issued on May 5, 1992 from Application No. 07/624,027, which was filed on December 7, 1990, and which was a continuation of Application No. 07/096,173, filed on September 11,1987. The joint inventors of the '493 patent are Dr. Roger Fu and Deborah Lidgate.

Mr. Silver:	And then, your honor, Dr. Mitra testified about some of the charts within and graphs you saw today. He testified about figures 3 and 4 on surface tension when Mr. Weed asked him questions; there was testimony on other pages as well, and those pages of the actual report are: 20, 22, 23, 24, 25, 31, and 36. And then at the end, 74 through 78, are just one of two sentences about each of the tables that he also testified about. **So I would offer those particular pages so that the record will be clear**, because his testimony relied upon it.
Ms. Haskett:	We would object to pages out of the actual report as being hearsay.
The Court:	I'll admit **them** as evidence of the opinion that he has given here. **I'll admit them**.

(R.T. 1891:12-1892:19) (emphasis added). Based on the foregoing except, Defendants only offered, and the Court only admitted (over Plaintiffs' objection), certain pages of Dr. Mitra's report. Accordingly, only pages 20, 22, 23, 24 ,25, 31, 36, 74, 75, 76, 77, 78, and exhibits A-N are part of the trial record. The Court therefore **GRANTS** Plaintiffs' Motion to strike all other potions of Dr. Mitra's report from the trial record. [1]

2. There are three types of claims in the '493 patent: claims to formulations (Claims 1-7), claims to methods of treating disease by using the formulations of Claims 1 -7 (Claims 8-14), and claims to a preservative system (Claims 15 and 16). Claims 1, 8, and 15 are the only independent claims in the '493 patent.

3. Independent Claim 1 claims:

> An ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation, comprising:
> an ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug in an effective amount for ophthalmic treatment between 0.001 % and 10.0% wt/vol;
> a quaternary ammonium preservative in an antimicrobially effective amount between 0.001 % and 1.0% wt/vol;
> an ethoxylated alky] phenol that conforms generally to the formula: C3H17C6H4(OCH2CH2)nOH where n has an average value of 40 in a stabilizing amount between 0.001% and 1.0% wt/vol; and an aqueous vehicle q.s. [quantity sufficient] to 100%.

(Trial Ex. 1 at SYN0000204, '493 patent at col. 8, ll 42-55

4. Dependent Claim 2 claims the formulation of Claim 1 wherein the quaternary ammonium

preservative is benzalkonium chloride ("BAC"); dependent Claim 3 claims the formulation of Claim 2 wherein the ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is selected from the group selected from ketorolac, indomethacin, flurbiprofen, and suprofen; dependent Claim 4 claims the formulation of Claim 3 wherein the ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is ketorolac tromethamine; and dependent Claim 5 claims the formulation of Claim 1, further comprising a chelating agent in an amount between 0.01% and 1.0% wt/vol; a tonicifier q.s. to achieve isotonicity with lacrimal fluid; and 1N NaOH or 1N HCI q.s. to adjust pH to 7.4±0.4. (Trial Ex.1 at SYN0000204, '493 patent at col 8,1156-68-col. 9, ll 1-10.)

5. Dependent Claims 6 and 7 claim specific compositions included within Claim 1, wherein the ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug (Claim 6) or ketorolac tromethamine (Claim 7) is present at 0.50% wt/vol; BAC is present at 0.02% wt/vol (of a 50% aqueous solution); Octoxynol 40 is present at 0.01% wt/vol (of a 70% aqueous solution); Na2EDTA is present at 0.10%; NaCl is present either at q.s. for isotonicity with lacrimal fluid (Claim 6) or at 0.79% wt/vol (Claim 7); the pH is adjusted to 7.4"0.4; and purified water is present at q.s. to 100%. Thus, Claims 6 and 7 are more specific than Claims 1-5, requiring formulations of specific ingredients in specific amounts. (Trial Ex. 1 at SYN0000205, '493 patent at col. 9 at 11-47.)

6. The method of treatment claims of the '493 patent begin with independent Claim 8. Claim 8 claims "[a] method of treating an ophthalmic disease caused by, associated with, or accompanied by inflammatory processes, comprising administering to a mammal suffering there from a formulation comprising" the formulation of Claim 1. (Trial Ex. 1, at SYN0000205, '493 patent at col. 9, ll 49-64.) Dependent Claims 9-14 claim the method of Claim 8 using the formulations of Claims 2-7, respectively. (Trial Ex. 1 at SYN0000205, 493 patent at col. 9, l165-col. 10, ll 50.) Thus, Claims 13 and 14 claim methods of treating ophthalmic disease by administering the very specifically claimed formulations of Claims 6 and 7.

7. Claims 15 and 16 are the preservative system claims. Independent Claim 15 claims "[a]n antimicrobially effective preservative system for an ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug formulation, comprising: a quaternary ammonium preservative in an antimicrobially effective amount between 0.001 % and 1.0% wt/vol of the formulation; and [Octoxynol 40] in a stabilizing amount between 0.001% and 1.0% wt/vol of the formulation." Dependent Claim 16 claims the preservative system of Claim 15 wherein the preservative is BAC. (Trial Ex. 1, at SYN0000205, '493 patent at col. 10, 11 52-65.)

8. An Information Disclosure Statement ("IDS") was filed along with both applications, identifying the following prior art: 4,087,539 (1978) Muchowski *et al.;* 4,089,969 (1978) Muchowski *et al;* 4,097,579

(1978) Muchowski *et at.;* 4,232,038 (1980) Kluge *et al.;* 4,336,151 (1982) Like *et al.;* 4,336,152 (1982) Like *et al.;* 4,545,151 (1984) Waterbury; "Influence of $(Ethoxy)_5$ Octyl Phenol on the Antibacterial Properties of Preservatives," M.T. Nadir, *et al, Journal of Pharmacy and Pharmacology,* Volume 29, Supplement, December 1977, page 67P; and "Ocufen (flurbiprofen sodium) 0.03% Liquifilm sterile ophthalmic solution, Allergan, product description sheet.

9. In addition, the examiner cited the following references in initially rejecting certain claims of the '493 patent under 35 U.S.C. § 103: 4,087,538 (1978) Portnoff; 4,230,724 (1980) Cooper *et al;* 4,474,751 (1984) Haslam *et al.;* 4,474,811 (1984) Masuda *et al.;* 4,500,538 (1985) Woltersdorf; 4,559,343 (1985) Han *et al.;* 4,607,038 (1986) Ogata *et al.;* Japanese Ref. No. 23,318 (1985); 4,349,563 (1982) Gilbert *et al.; The Condensed Chemical Dictionary,* Seventh Ed.; *McCutcheon's "Emulsifiers and Detergents"* (1982) (*"McCutcheon's");* "The Synergistic Effects of Nonionic Surfactants Upon Cationic Germicidal Agents," Schmolka (1973). (Trial Exs. 024 at SYN0000245-48, 035 at SYN0000034-44, SYN0000050-52.)

10. A person of ordinary skill in the art at the time of the invention is a person having a Bachelor's or Master's degree in the pharmaceutical sciences and having three to five years of experience working in the field -under the supervision of a person having a Ph.D. in the pharmaceutical sciences. (R.T. 1707:11-24; DOB at 5 n.3.)

2. The Prior Art References

11. Plaintiffs assert that at trial, Defendants only asserted that the combination of U.S. Patent No. 4,545,151 to Waterbury, U.S. Patent No. 4,349,563 to Gilbert *et al.*, and U.S. Patent No. 4,559,343 to Han *et ah,* rendered obvious the claims of the '493 patent. Defendants, however, contend that in addition to these references, they also relied on: (1) *McCutcheon 's;* (2) the Pharmaceutical Expert Report; (3) *Grant and Hackh's Chemical Dictionary;* (4) the GAF product sheet; (5) the Cosmetic Dictionary; (6) the Nadir reference (Trial Ex. YK); (7) the Schmolka reference; and (8) the Condensed Chemical Dictionary. Plaintiff does not dispute that each of the references that Defendants cited are in the trial record. Because the inclusion of the additional references cited by Defendants does not affect the Court's ultimate determination on the issue of obviousness, the Court will consider all the references that Defendants have cited. However, based on its review of the trial record, the Court finds that Defendants' obviousness challenge relied primarily on the Waterbury patent, the Gilbert patent, the Han patent, and *McCutcheon*'s.

12. U.S. Patent No. 4,454,151 to Waterbury (the "151 patent" and/or the "Waterbury patent") defines a number of non-steroidal anti-inflammatory drugs that were found to be efficacious in the treatment of inflammatory diseases.

13. The Waterbury patent does not discuss the concepts of long-term stability or anti-microbial effectiveness and does not discuss any problem of

interaction or complexation between BAC and ketorolac tromethamine. It also does not discuss the use of EDTA or any other chelating agent. (Trial Ex. 004; R.T. 1158:1-16, 1159:2511 60:3, 1707:25-1710:6.)

14. Although the only example formulation in the Waterbury patent, Example 1 ("Composition of Ophthalmic Solutions for Topical Administration to the Eye"), does not include a surfactant in its composition, the Waterbury patent does disclose the use of the surfactant Polysorbate 80 (also referred to as "Tween 80"). The Waterbury patent, however, discloses Polysorbate 80 as a member in a list of stabilizers - not surfactants. (Trial Ex. 004 at 13:44-48, 56-57.) The only other stabilizer disclosed in that list is glycerin, which is not a surfactant. (R.T. 1709:5-10.)

15. U.S. Patent No. 4,349,563 to Gilbert (the '"563 patent" and/or the "Gilbert patent") teaches the topical administration to the eye of non-steroidal anti-inflammatory agents, which as a class previously were thought to be ineffective in treating ocular inflammation. The Gilbert patent teaches that NSAIDs for ocular administration should include various ingredients other than the non-steroidal anti-inflammatory agent itself, such as antimicrobial agents, antioxidants, and metal ion sequestering agents. The Gilbert patent does not, however, mention ketorolac tromethamine. (Trial Ex. WJ.)

16. Although the Gilbert patent states that "the presence of a stabilizer is not preferred," the patent

does teach the optional inclusion of Tween or Pluronic surfactants, and specifies Polysorbate 80. The Gilbert patent does not mention Octoxynol 40, and does not discuss the concepts of long-term stability or anti-microbial effectiveness or any problem of interaction or complexation between BAC and NSAIDs. (R.T. 1711:20-1712:7.) It also does not discuss the use of EDTA or any other chelating agent. (Trial Ex. WJ.)

17. U.S. Patent No. 4,559,343 to Han, *et al.* (the "'343 patent" and/or the "Han patent") discloses that the addition of xanthines, such as caffeine, to ophthalmic solutions of acidic NSAIDs helps to reduce the irritation associated with the NSAIDs. (Trail Ex. AK.) Specifically, the Han patent claims an aqueous, nonirritating, nonsteroidal ophthalmic composition comprising the NSAID suprofen, a xanthine, a preservative, and a buffer, as well as methods for using this composition. *(Id.)* Two of the examples of the Han patent disclose the use of NSAIDs with either BAC or thimerosal and either Pluronic F127 or tyloxapol, but do not indicate whether Pluronic F127 or tyloxapol are being used as stabilizers, or indicate what role these surfactants play in the example compositions at all. (*Id.)* The Han patent does not discuss the concepts of long-term stability or anti-microbial effectiveness and does not discuss any problem of interaction or complexation between BAC and ketorolac tromethamine. It also does not discuss the use of EDTA or any other chelating agent. *(Id.)*

18. *McCutcheon's* is a compendium of a large number of emulsifiers and detergents. (Trial Ex.

AL.) It describes Igepal CA-897 (Octoxynol 40) as an "Enrulsifier, stabilizer." However, *McCutcheon 's* does not disclose the use of Octoxynol 40 in a pharmaceutical. *(Id.)* There is nothing in *McCutcheon's* that suggests that Octoxynol 40 could successfully be used to solve the interaction between a carboxyl-group-containing NSAID and a quaternary ammonium preservative. There is nothing in *McCutcheon's* that suggests that Octoxynol 40 could safely be used in a pharmaceutical product or in an ophthalmic formulation. There is nothing in *McCutcheon's* that suggests that the use of Octoxynol 40 would preserve the anti-microbial effectiveness of a preservative.

19. None of the prior art references cited by Defendants disclose any functional equivalence between Octoxynol 40 and any of the surfactants disclosed by the Waterbury, Gilbert or Han patents.

20. Apart from the September 1987 Pharmaceutical Report authored by Dr. Fu and Ms. Lidgate ("the Syntex Report"), none of the prior art references cited by Defendants mention Octoxynol 40., except for *McCutcheon's*. Defendants' expert, Dr. Mitra, provided no testimony at all regarding *McCutcheon's*.

21. Plaintiffs' expert, Dr. Stella, testified that although *McCutcheon's* refers to Octoxynol 40 as an emulsifier/stabilizer, it uses those words in the context of mixing and stabilizing a non-water-miscible substance and water. This is an entirely different context from the use of those words in the '493 patent, which discloses the use of Octoxynol 40

as a stabilizer in a solution consisting of an NSAID and a quaternary ammonium preservative. (R.T. 1714:11-19; Trial Ex. 1, claim I.)

22. Dr. Stella also testified that there was nothing in *McCutcheon's* that would have motivated one of ordinary skill in the art to combine it with the other prior art references to arrive at the patented inventions. (R.T. 1715:17-22.)

23. Significantly, Defendants have not identified any prior art reference that either discloses or suggests: (a) that Octoxynol 40 be used in an ophthalmic formulation; (b) that it be used in a preservative system with a quaternary ammonium preservative; (c) that it be used in a formulation with a quaternary ammonium preservative, such as BAC; (d) that it be used in a formulation with a carboxyl group-containing NSAID, such as ketorolac tromethamine; (e) that it be used to prevent the formation of a complex between a carboxyl group-containing NSAID and a quaternary ammonium preservative; or (f) that it would act to maintain the antimicrobial effectiveness of a quaternary ammonium preservative, such as BAC, in an ophthalmic formulation.

3. The Prosecution History of the '493 Patent

24. As previously indicated, an IDS was filed along with both Application No. 07/096,173 and

Application No. 07/624,027, which led to the issuance of the '493 patent, identifying the following prior art: 4,087,539 (1978) Muchowski *et al.;* 4,089,969 (1978) Muchowski *et al.;* 4,097,579 (1978) Muchowski *et al.;* 4,232,038 (1980) Kluge *et al.;* 4,336,151 (1982) Like *et al;* 4,336,152 (1982) Like *et a.l;* 4,545,151 (1984) Waterbury; "Influence of $(Ethoxy)_5$ Octyl Phenol on the Antibacterial Properties of Preservatives," M.T. Nadir, *et al, Journal of Pharmacy and Pharmacology,* Volume 29, Supplement, December 1977, page 67P; and "Ocufen (flurbiprofen sodium) 0.03% Liquifilm sterile ophthalmic solution, Allergan, product description sheet.

25. In addition, the examiner cited the following references in initially rejecting certain claims of the '493 patent under 35 U.S.C. § 103: 4,087,538 (1978) Portnoff; 4,230,724 (1980) Cooper *et al.;* 4,474,751 (1984) Haslam *et al.;* 4,474,811 (1984) Masuda *et al.;* 4,500,538 (1985) Woltersdorf; 4,559,343 (1985) Han *et al;* 4,607,038 (1986) Ogata *et al.;* Japanese Ref. No; 23,318 (1985); 4,349,563 (1982) Gilbert *et al; The Condensed Chemical Dictionary,* Seventh Ed.; *McCutcheon's "Emulsifiers and Detergents"* (1982); "The Synergistic Effects of Nonionic Surfactants Upon Cationic Germicidal Agents," Schmolka (1973). (Trial Exs. 024 at SYN 0000245-48,035 at SYN 0000034-44, SYN0000050-52.)

26. The results of Ms. Lidgate's study of formulations containing ketorolac tromethamine, BAC, and three different surfactants-Octoxynol 40, Tween 80, and Myrj 52-were also disclosed to the Examiner during the examination of the parent

Application No. 07/096,173. These results showed that solutions containing Octoxynol 40 remained clear under a variety of storage conditions while solutions containing Tween 80 and Myrj 52 became turbid. (Trial Exs. 204, 205, 009, 024 at SYN0000280, 035 at SYN0000057-64; RT. 695:1-701:14, 761:2-762:9, 769:11-770:25.)

27. The examiner of Application No. 07/096,173 criticized the data comparing Octoxynol 40, Tween 80, and Myrj 52 for four reasons: (1) the data did not compare Octoxynol 40 to the surfactants of the primary references; (2) the concentration of Octoxynol 40 was greater than the concentrations of the other surfactants; (3) the data was not commensurate with the then-pending claims, which did not set proportions for the components of the formulations; and (4) the data was not in declaration form. (Trial Ex. 24 at SYN0000288.)

28. The examiner's criticism number (1), that the surfactants of the primary references were overlooked, is no longer relevant at this stage in the proceedings. The data before the examiner compared Octoxynol 40 to the surfactant most mentioned in the primary references-Tween 80. Furthermore, the Court-unlike the examiner-also has before it evidence that Ms. Pulsipher tried to use the Pluronic F127 of Han, as well as Pluronic Fl 68, to solve the ketorolac tromethamine/BAC turbidity problem, and found that these surfactants were unable to do what Octoxynol 40 later was discovered to do-namely, keep a solution of ketorolac tromethamine and BAC stable under variable conditions. (R.T. 350:5-375:15.)

29. The examiner's criticism number (2), regarding the relative concentrations of the surfactants used in the experiments was that, whereas the concentrations of Octoxynol 40 are listed as 0.004% and 0.02%, the concentrations of the other surfactants are listed as 0.0035% and 0.01% for Tween 80 and 0.0015% and 0.01% for Myrj 52. Therefore, the "high" and "low" concentrations of Octoxynol 40 are higher, respectively, than the "high" and "low" concentrations of the other surfactants. However, comparing the results for the "low" concentration of Octoxynol 40 (the 0.004% column) with the "high" concentrations of Tween 80 and Myrj 52 (the two columns labeled 0.01%), indicates that Octoxynol 40 still outperforms the other surfactants. In other words, taking, for example, the observations made after one month at 40°C, a concentration of 0.004% of Octoxynol 40 was able to keep the solution clear, whereas 0.01% concentrations of Tween 80 and Myrj 52-that is, concentrations two and a half times higher than the Octoxynol 40 concentration-resulted in solutions that were "very turbid" and "turbid," respectively. (Trial Ex. 24 at SYN0000280.)

30. The examiner's criticism number (3), regarding the then-pending claims, is irrelevant at this stage in the proceedings. Unlike the claims that were pending at the time of the examiner's comments, the claims of the '493 patent, as finally issued and as asserted in this lawsuit, do set forth proportions of the formulation components. *(See* Trial Ex. 001.)

31. Similarly, the examiner's criticism number (4), that the data from Ms. Lidgate's tests was not in declaration form was specific to the prosecution context. The results of Ms. Lidgate's tests, supported by sworn trial testimony from Ms. Lidgate, are in the trial record. Ms. Lidgate's test data compares the performance of Octoxynol 40 with the performance of other micelle-forming, non-ionic surfactants, which Dr. Mitra says should all perform "equally well" and which Defendants have asserted to be the closest prior art to the '493 patent.

32. Defendants have argued that the data comparing Octoxynol 40, Tween 80, and Myrj 52 should be disregarded because it contains inconsistencies. Defendants base this argument on the fact that the data shows that all solutions were clear at 60°C, both at 1 month and at 5 months, thus showing that the turbidity of those particular solutions did not increase with time. Defendants have also pointed to the fact that the Tween 80 solutions at 40°C were described as "very turbid" at 1 month, but only "turbid" at 5 months, indicating that turbidity may have decreased over time. However, Defendants fail to take into account that all of the solutions containing Octoxynol 40 remained clear, at all temperatures and over all time periods, while the solutions containing Tween 80 and Myrj 52 became turbid under several different time and temperature conditions. (Trial Ex. 24 at SYN0000280.) This demonstrates that the solutions containing Octoxynol 40 had better "robust" stability under a variety of conditions than did the solutions containing Tween 80 and Myrj 52.

33. Defendants have also argued that because the original claims of Application No. 07/096,173 claimed "a stabilizing amount of a nonionic surfactant," Trial Ex. 24 at SYN0000235, the applicants admitted to the PTO that all nonionic surfactants are the same. The applicants, however, made no such admission and in fact subsequently narrowed the claims to just the use of Octoxynol 40. The prosecution history in its entirety, therefore, supports a conclusion that the applicants did not believe all nonionic surfactants to be the same.

34. Defendants also point to the applicants' statement in the prosecution history that "such compounds [non-ionic polyoxyethylated octylphenol surfactants] are generally known to those skilled in the art as useful surfactant compounds." (Trial Ex. 24 at SYN0000259.) However, the fact that such compounds may have been known to be "useful surfactant compounds," does not support the inference that they were known, prior to the inventions of the '493 patent, to be useful in ophthalmic formulations or in solubilizing NSAID/BAC complexes. In fact, several other types of known surfactant compounds were specifically found by the Syntex scientists not to be useful in ketorolac tromethamine/BAC formulations.

35. On March 5, 1991, the PTO issued a rejection of all of the claims of Application No. 07/624,027 as obvious over the prior art. The Examiner noted that the Gilbert and Han patents both taught the use of "nonionic surfactants" as stabilizing agents and stated that any non-ionic surfactant would lead to

"better solubilization of said quaternary ammonium compound." (Trial Ex. 35 at SYN0000048.)

36. The examiner of Application No. 07/624,027 also specifically rejected claims 37 and 38 as obvious over the Nadir and Schmolka references. The Nadir reference suggested the use of Octoxynol 5 in conjunction with antibacterial preservatives. (Trial Ex. 035 at SYN0000048, SYN0000090; RT. 766:3-768:22, 771:1-772:4.)

37. In response to the March 5, 1991 rejection, on September 5, 1991, Dr. Derek Freyberg, in-house counsel for Syntex submitted an Amendment of the claims. Specifically, in response to the Examiner's rejection of claims 37 and 38 over the Nadir reference, Dr. Freyberg submitted a declaration of Ms. Lidgate (the "Lidgate Declaration"). The Lidgate Declaration included the results of a test performed by Ms. Lidgate that compared formulations containing Octoxynol 40, Octoxynol 5, and Octoxynol 3. (Trial Ex. 035 at SYN0000057-64; R.T. 769:11-770:25.)

38. The September 5, 1991 Amendment also stated as follows:

> Applicants have shown in the prosecution of the parent to this application that other nonionic surfactants, such as Tween and Myrj, fail to act as stabilizers in the claimed formulations; and the enclosed Declaration of Deborah M. Lidgate

> demonstrates that certain octoxynols are unsatisfactory.

Thus, the Amendment attempted to convince the Examiner that he was wrong in treating all nonionic surfactants alike because at least some surfactants, including certain octoxynols, would not work to stabilize the claimed formulations. (Trial Ex: 035 at SYN0000062.)

39. When Ms. Lidgate turned her data from the experiment in question over to Syntex's patent department, the data included the results of experiments on formulations containing Octoxynol 40, Octoxynol 5, Octoxynol 3, and Octoxynol 12.5. Included in those results was Ms. Lidgate's observation that, after three months of stability testing, the fonnulations containing Octoxynol 40 and Octoxynol 12.5 looked equivalent. (R.T. 658:1-660:23.)

40. Although Ms. Lidgate noted that the formulations containing Octoxynol 40 and Octoxynol 12.5 looked equivalent, she did not conclude that they were equivalent in any other respect. In particular, Ms. Lidgate had no evidence that the formulation containing Octoxynol 12.5 would pass the "USP challenge" test for antibacterial effectiveness. (R.T. 651:13-652:12, 660:16-661:8.)

41. While Ms. Lidgate did not make the decision as to which of the octoxynols would be included in the Lidgate Declaration, she believed the Declaration to be accurate and truthful at the time that she signed it. Ms. Lidgate testified that she had

no reservations about the fact that the Declaration did not mention Octoxynol 12.5 because the purpose of the Declaration was to show that not all octoxynols would be suitable for use in the patented formulation. (RT. 661:9662:6.)

42. Dr. Freyberg did not include any reference to Octoxynol 12.5 in the Lidgate Declaration because the purpose of the Declaration was to compare the invention with the prior art cited by the exarainer-that is, Octoxynol 5. The examiner cited no prior art reference that described an ophthalmic formulation using Octoxynol 12.5, and there is no evidence in the record of the existence of any such prior art reference. (RT. 772:5-774:13.)

43. The examiner mailed a notice of allowance of all claims on December 3, 1991. (Trial Ex. 131 at SYN0000066.) The '493 patent issued on May 5, 1992.

4. Use of Octoxynol 40 in Pharmaceuticals

44. In its December 29 Order, the Court found that "[n]o pharmaceutical formulation other than ACULAR® has ever included Octoxynol 40." (Doc. #350 at 126.) In its opinion remanding the case to this Court, the Federal Circuit directed the Court to reconsider that finding in light of the Syntex report. *Syntex,* 407 F.3d at 1379.

45. The Syntex Report states that Octoxynol 40 was a well known ingredient in pharmaceutical products. (Trial Ex. 303 at SYN11264.) At trial,

however, Ms. Lidgate could not recall the basis for this statement in the Syntex Report. (R.T. 580:4-21.) Likewise, Dr. Fu testified that he had no knowledge of the statement in the Report. (R.T. 830:15-21.) There was no evidence as to what products the Syntex Report referred to.

46. Additionally, other evidence on the issue contradicted the statement from the Syntex Report. Specifically, Defendants' expert, Dr. Mitra, testified that, prior to its use in ACULAR®, Octoxynol 40 was never used in a pharmaceutical formulation. (R.T. 1165:3-14.) Dr. Mitra also testified that Octoxynol 40 was not used in any pharmaceutical product on the market currently except for ACULAR®. *(Id.)* Octoxynol 40 is not listed in the 1986 Handbook of Pharmaceutical Excipients. (R.T. 1229:7-13.) Thus, no evidence corroborates the statement in the Syntex Report concerning Octoxynol 40, and significant evidence contradicts the statement.

47. Defendants argue that three additional references demonstrate that Octoxynol 40 was "well known in the art." Specifically, Defendants argued that "Grant & Hackh's Chemical Dictionary, the GAF product sheet and the Cosmetic Dictionary all show that O40 was well known in the art." (DRP at 8.) Defendants further argued that "Syntex admitted that [these references] all show that O40 was well known in the art" during prosecution. *(Id.)*

48. Contrary to Defendants' characterization, the applicants did not admit during prosecution that these three references show that Octoxynol 40 was well known in the art. The examiner initially

rejected the claims for lack of a written description because "[t]he specification does not adequately define the term Octoxynol 40." (Trial Ex. 24 at SYN0000268.) In response, the applicants cited to Grant & Hackh's Chemical Dictionary and to the GAF product sheet, not as prior art, but as evidence that in reading the issued patent, one skilled in the art would recognize Octoxynol 40 as a surfactant compound having a particular chemical formulation. (Trial Ex. 24 at SYN0000276-77; Trial Ex. 35 at SYN000033.) The applicants cited to the "Cosmetic Ingredients Dictionary" merely to inform the examiner that "'octoxynol 40' is not a trademark." (Trial Ex. 35 at SYN000033.) The applicants did not state that these references show that Octoxynol 40 was well known in pharmaceutical formulations or, in particular, as a stabilizer in an NSAID and BAC formulation. *(Id.)* In fact, it has not been shown that any of these references are even from the field of pharmacology.

49. Based on the evidence presented, the Court finds that Octoxynol 40 may have been used in one or more unknown "pharmaceutical products" prior to the time the '493 patent application was filed. This fact is accorded only limited weight, however, because there was no evidence suggesting what these "pharmaceutical products" might have been or what the particular use of Octoxynol 40 in those products, might have suggested to one of ordinary skill in the art. Moreover, the Court finds that there is no evidence that Octoxynol 40 was used in an ophthalmic product or formulation before the inventions of the '493 patent.

5. Unexpected Results

50. In its December 29 Order, the Court concluded that the patented inventions produced unexpected results. (Doc. #350 at 153.) In its opinion remanding the case to this Court, the Federal Circuit directed this Court to reconsider that finding in light of the prosecution history and the testimony of Dr. Mitra. *Syntex*, 407 F.3d at 1382-83. In particular, the Federal Circuit directed this Court to reevaluate the criticisms by the first examiner of the data comparing Octoxynol 40, Tween 80, and Myrj 52, and to reconsider the fact that, during prosecution, the applicants did not submit Ms. Lidgate's results showing that "octoxynol 12.5 and octoxynol 40 produced test samples that 'looked equivalent at all temperatures.'" *Id.*, 407 F.3d at 1382-83. The Federal Circuit also instructed this Court to consider Dr. Mitra's testimony regarding the substitutability of various surfactants in connection with the unexpected results inquiry. *Id.* at 1380-82.

51. As indicated above, the examiner of Application No. 07/096,173 criticized the data comparing Octoxynol 40, Tween 80, and Myrj 52 for four reasons: (1) the data did not compare Octoxynol 40 to the surfactants of the primary references; (2) the concentration of Octoxynol 40 was greater than the concentrations of the other surfactants; (3) the data was not commensurate with the then-pending claims, which did not set proportions for the components of the formulations; and (4) the data was not in declaration form. (Trial Ex. 24 at SYN0000288.)

52. The data in the prosecution history showing that Octoxynol 40 outperformed Tween 80 and Myrj 52 is persuasive on the issue of unexpected results and is not rendered less so by any of the criticisms on the part of the examiner of the 07/096,173 application.

53. The Court has also considered Ms. Lidgate's test results regarding Octoxynol 12.5 and concludes that they do not undermine a finding that the patented inventions produced unexpected results.

54. As previously indicated, although Ms. Lidgate concluded that formulations containing Octoxynol 40 and Octoxynol 12.5 were equivalent from a visual perspective, she did not determine that they were equivalent in any other respect. Particularly, the testing that Ms. Lidgate performed did not provide data regarding the stability of Octoxynol 12.5 or that it would have been antimicrobially effective. (R.T. 652:7-12; 661:4-5.)

55. Further, even if Octoxynol 12.5 was found to perform as well in the patented formulations as Octoxynol 40 - an assumption that cannot be confirmed due to the absence of antimicrobial data regarding Octoxynol 12.5 - this would not detract from the unexpected results demonstrated by the data comparing Octoxynol 40, Tween 80, and Myrj 52. Particularly, it would still be unexpected to find that Octoxynol 40 outperformed these other well-known surfactants, which were disclosed in the prior art references, even if some other surfactants, such as Octoxynol 12.5, were capable of doing the same.

56. Defendants have argued that Ms. Lidgate's experiments that led to the submission of the Lidgate Declaration improperly lacked a "control formulation"- that is, a formulation to which other formulations are compared. In fact, the formulation containing Octoxynol 40 was the formulation that other formulations were being compared against, and it therefore acted as the "control" formulation in the experiments. (R.T. 621:6-622:37.)

57. Dr. Mitra's testimony that a surfactant's micelle-forming and non-ionic properties would necessarily enable that surfactant to have stabilizing abilities, and that therefore it was to be expected that Octoxynol 40 would function "equally [as] well" as other micelle-forming, non-ionic surfactants in stabilizing ophthalmic formulations, (R.T. at 1016:1-1018:15; *id.* at 1054:6-24; *id.* at 1122:14-1123:13; *id.* at 1129:3-16), fails on two levels to support a finding that Octoxynol 40's performance was not expected. First, if the state of knowledge at the time the inventions was that all micelle-forming, non-ionic surfactants would work "equally well," then Plaintiffs' evidence of the results of testing carried out by Ms. Lidgate - showing that Octoxynol 40 outperformed two other much more well-known micelle-forming, non-ionic surfactants - is highly unexpected. (R.T. 695:1-701:14; Trial Exs. 204 & 205.) Moreover, the corollary to Dr. Mitra's substitutability theory, namely that Octoxynol 40 would be expected to function well as an ophthalmic formulation stabilizer, cannot be attributed to the state of the art at the time the '493 inventions were made. Neither the test results upon which Dr. Mitra

based his conclusions, nor any similar test results, were known at the time of the patented inventions. The only data in evidence comparing the performance of Octoxynol 40 to surfactants disclosed in the prior art patents prior to the time of the patented inventions is the data from Ms. Lidgate's tests comparing the performance of Octoxynol 40 with the performance of Tween 80 and Myrj 52-other micelle-forming, non-ionic surfactants, which Dr. Mitra opined should perform "equally well." That data shows that Octoxynol 40 at a concentration of 0.004% outperforms Tween 80 and Myrj 50 at the significantly higher concentration of 0.01%. (Trial Ex. 24 at SYN0000280.)

58. In addition to the fact that Defendants' test results conducted years after the prosecution of the '493 patent are not relevant to the expectations of those skilled in the art at the time of the patented inventions, those results are also entitled only to limited weight due to the fact that a variety of grades, sources, or types of ingredients were not tested. Moreover, because the homolog content of the BAC used in a formulation has a significant effect on the degree of complexation between ketorolac tromethamine and BAC, Defendants cannot show that the results of their tests would have been the same had a different grade of BAC been used. Likewise, Defendants cannot show that the results of their tests would have been the same had a different source of ketorolac tromethamine been used. Finally, Defendants cannot show that the results of their tests NSAIDs or all quaternary ammonium preservatives been tested.

59. Defendants further failed to establish that the ingredients used in their tests were substantially similar to the ingredients used by the Syntex researchers at the time of the application for the '493 patent. Therefore, the Court accords only limited weight to the results of tests that used ingredients that may have been different from those available at the time of the patent application.

60. Taking the foregoing findings into consideration, the Court finds that Defendants have failed to overcome the Plaintiffs' showing that the patented inventions produced unexpected results. This finding supports a conclusion that the patented inventions are non-obvious.

6. Motivation to Combine

61. In its December 29 Order, the Court found that the three prior art references asserted by Defendant - Waterbury, Gilbert, and Han - teach away from the use of Octoxynol 40 in an ophthalmic formulation. (Doc. #350 at 141.) In its opinion remanding the case to this Court, the Federal Circuit directed the Court to reconsider whether Defendants have adduced clear and convincing evidence that there would have been a motivation to combine these references with the understanding that the references do not teach away from the use of Octoxynol 40. *Syntex,* 407 F.3d at 1380.

62. Reconsidering this issue, while the prior art references may not teach away from the use of Octoxynol 40 in an ophthalmic formulation, the record fails to establish by clear and convincing

evidence that any of the references suggest, teach, or motivate use of Octoxynol 40 in an ophthalmic formulation. Particularly, Waterbury expressly teaches the use of Polysorbate 80. Han, in comparison, teaches the use of nonionic surfactants, generally. Gilbert discloses ophthalmic formulations that may contain a stabilizer, only some of which are nonionic surfactants. Thus, the references relied upon by Defendants, whether examined in isolation or collectively, would not have suggested a motivation to combine to one skilled in the art at the time of the patent application.

63. Defendants rely heavily upon the testimony of Dr. Mitra to support their argument that there would have been a motivation to substitute Octoxynol 40 for any of the surfactants disclosed in the Waterbury, Gilbert, and Han patents at the time of the '493 patent inventions. Specifically, Defendants proffer Dr. Mitra's testimony that because "Octoxynol 40 was very well known in [the] cosmetic industry and has been used in many products," it "will be easy" to substitute Octoxynol 40 for the Polysorbate 80 of the Waterbury patent. (R.T. 1143:13-1144:3.)

64. Dr. Mitra testified that one would be motivated to substitute Octoxynol 40 for Polysorbate 80 based on his theory that all non-ionic water-soluble surfactants work equally well in stabilizing solutions made up of an NSAID and a quaternary ammonium preservative. (R.T. 1035:25-1038:18.)

65. In arguing that all surfactants work equally well, Defendants point to statements in Dr. Mitra's

expert report that the Federal Circuit identified as potentially relevant to the issue of "unexpected results." *See Syntex,* 407 F.3d at 1383 nn.10 & 11. Defendants argue that these statements are relevant to the separate issue of a motivation to combine.

66. For example, Dr. Mitra stated in his expert report that "[t]he Waterbury '151 patent shows that the non-ionic surfactant Polysorbate 80 solubilizes BAC. Therefore, one would expect that other non-ionic surfactants would work equally as well and one would thus look to other patents/publications which show that other non-ionic surfactants such as octoxynol 40, function as a surfactant." (Trial Ex. SI 348 (quoted in *Syntex,* 407 F.3d at 1381 n.11).)

67. Reviewing the Federal Circuit's Opinion, there is some ambiguity in the Circuit's language as to whether it determined that statements in Dr. Mitra's expert report are relevant to the motivation to combine issue. As the Court interprets the Federal Circuit's decision, the Circuit did not hold that these statements are relevant to the issue of motivation to combine, but, rather, that they are *potentially* relevant to unexpected results. *Syntex,* 407 F.3d at 1381. Even assuming the statements are relevant on the motivation to combine issue and are part of the pages admitted during trial, the Court accords them little probative weight. Particularly, contrary to Dr. Mitra's statement, the Waterbury patent does not discuss any problem of interaction or complexation between BAC and ketorolac tromethamine, and does not include Polysorbate 80 in an example formulation, and therefore does not show "that the

non-ionic surfactant Polysorbate 80 solubilizes BAC."

68. Further, the Court finds Dr. Mitra's opinion that all water-soluble non-ionic surfactants would have worked equally well in the patented formulations unpersuasive for several reasons.

69. First, Defendants' experiments that provided the basis for Dr. Mitra's opinions regarding the "substitutability" of non-ionic water-soluble surfactants were all conducted years after the filing of the '493 patent applications. (R.T. 1004:16-19.) Defendants offered no evidence that the results of any like experiments were known at the time of the patented inventions. The experiments therefore are not probative of the knowledge of one of ordinary skill at the time of the inventions.

70. Second, Dr. Mitra's opinion that all water-soluble non-ionic surfactants work equally well also lacks evidentiary support because the experiments offered by Defendants at trial in support of his opinion suffer from critical methodological flaws. In particular, the stability of a solution of ketorolac tromethamine and BAC will be heavily dependent on the type of BAC that is used. Because BAC ts not a pure substance, but is made up of amixture of "homologs," *i.e.*, molecules that are similar but that have varying lengths, the source of the particular BAC that is used will have a significant effect on the concentrations of ketorolac tromethamine and BAC at which a complex is formed. (R.T. 1647:24-1649:1,1670:2-1676:4; Trial Ex. 306.) The tests presented by Defendants that evaluated the effect of

Octoxynol 40 and/or compared the effect of Octoxynol 40 with the effects of other surfactants all used BAC and ketorolac tromethamine from a single source. Novex Pharma, in general, did not account for the possibility that the particular homolog content of the BAC that it was affecting the stability of the formulations or whether any lot-to-lot variability in the ketorolac tromethamine was having an effect. On the one occasion on which Dr. Mitra tested the effect of using different types of BAC, he found that the type of BAC used had a significant effect on the degree of complexation between ketorolac tromethamine and BAC. (R.T 1202:17-1207:25.) Similarly, a test performed by Cynthia Pulsipher, a scientist at Syntex, confirmed that variability between lots of ketorolac tromethamine could affect the stability of the resulting formulation. (Trial Ex. 209; R.T. 186:25-187:7, 196:2200:12,381:3-392:5.)

71. Because Defendants have failed to show that the ingredients used in the tests performed by Dr. Mitra and Novex Pharma were substantially similar to the ingredients used by the Syntex researchers the Court accords their test results evaluating the effect of Octoxynol 40 and/or comparing the effect of Octoxynol 40 with the effects of other surfactants only to limited weight. Particularly, because the homolog content of the BAC used in a formulation has a significant effect on the degree of complexation between ketorolac tromethamine and BAC, Defendants cannot show that the results of their tests would have been the same had a different grade of BAC been used. Likewise, Defendants cannot show that the results of their tests would have been the same had a different source of

ketorolac tromethamine been used. Cumulatively, these weaknesses in Defendants' tests significantly undermine the validity of their data.

72. Dr. Mitra's critique of Syntex's testing relating to turbidity is also unpersuasive. Specifically, Dr. Mitra accounted for the variation in the turbidity results observed by the Syntex scientists by opining that, as more tromethamine is added to a solution containing ketorolac tromethamine and BAC, the trometharaine ions drain the ketorolac ions from the solution, forcing the ketorolac/BAC precipitate to dissolve. (R.T. 1010:34-1013:20.)

73. Dr. Stella, however, testified that this theory was "fundamentally unsound." (R.T. 1716:9-1717-4.) Specifically, Dr. Stella pointed out that more tromethamine ions could not be added to the solution without, at the same time, adding more ketorolac ions. Therefore, the continued addition of ketorolac tromethamine would not serve to drain the ketorolac ions from the solution and would not shift the equilibrium such that the precipitate would dissolve. (R.T. 1716:9-1717:19.) Dr. Mitra did not provide a viable explanation as to how more tromethamine ions would be introduced to the solution without the accompanying ketorolac ions. His inability to proffer such an explanation seriously undermines the persuasiveness of his theory with respect to Syntex's tests.

74. With respect to Dr. Mitra's opinion that non-ionic, water-soluble surfactants act alike, the Court also takes notice of evidence in the record calling

this opinion into question. Specifically, the "Surfactant Systems" treatise lists data showing that different surfactants can have widely different abilities to solubilize the same compound. (Trial Ex. 033 at 343, Table 6.23(a).) In fact, that data shows for a particular compound a 17-fold variation in the ability of several different surfactants (including four types of polysorbate) to solubilize the compound in question. (*Id.* (showing, in the right-hand column, solubilities of from 0.04 to 0.68 moles of compound per mole of surfactant).) Such a wide variation in the ability to solubilize demonstrates that all water-soluble, micelle-forming, non-ionic surfactants do not perform alike. Furthermore, the "Surfactant Systems" treatise explicitly recognizes the presence of "variations in the properties of commercial surface-active agents," *id.* at 344, confirming the variability in the performance of different surfactants.

75. Plaintiffs have also offered Dr. Stella's testimony which contradicts Dr. Mitra's theory regarding the substitutability of surfactants. Notably, Dr. Stella testified that a surfactant's critical micelle concentration, *i.e.*, the concentration at which a surfactant forms micelles, varies depending on both the structure of the surfactant - namely, the length of the alkyl chain groups and the polarity of the head group - and the structural elements of the material the surfactant is attempting to solubilize. (R.T. 1692:5-23.) This critical micelle concentration will also vary with temperature, with the addition of electrolytes, and with the presence of other ingredients in a formulation. (R.T. 1846:24-1848:1 (Mitra).) Because

of the high variability and sensitivity of surfactants' critical micelle concentrations, Dr. Stella testified that different surfactants will differ widely in their abilities to stabilize a given structure or solution. (R.T. 1692:24-1693:9.)

76. Dr. Stella also criticized Dr. Mitra's opinion for failing to take into account how the variations in other parameters, such as differences in BAC and environmental factors, affected when turbidity and haziness cleared. (R.T. 1717:5-9.)

77. Dr. Stella further opined that Dr. Mitra's theory failed to explain the variations in the test results because it did not take into account the effect of the variations seen between the Syntex data, the Novex data, and Dr. Mitra's own data. (R.T. 1717:11-19.)

78. Overall, as the foregoing findings illustrate, Dr. Mitra's opinions are based on tests that post-date the filing of the '493 patent applications; suffer from methodological flaws, and are directly contradicted by Dr. Stella's testimony. Taken together, these factors undermine the validity of Dr. Mitra's opinions and compel the Court to find that his testimony is not credible. In contrast, the Court finds Dr. Stella's opinions and supporting rationales to be persuasive. The Court therefore rejects Dr. Mitra's testimony on whether a motivation to combine existed.

7. The Dependent Claims of the '493 Patent

79. The dependent claims of the '493 patent disclose more detailed inventions than the independent claims, including: pharmaceutical compositions containing specific quaternary ammonium preservatives and NSAIDS (claims 2-3); pharmaceutical compositions containing specific proportions of chelating agents and other ingredients (claims 4-7); specific method claims (claims 9-14); and a preservative system containing BAC and a preservative (claim 16). (Trial Ex. 001.)

80. The subjects of the dependent claims-the identity and concentration of the NSAIDs, the identity and concentration of the preservative, the identity, presence and concentrations of chelating agents and salt, and pH-all have significant effect on the stability and antimicrobial effectiveness of the ophthalmic solution. (R.T. 3636:11-1637:19, 1642:23-1645:9, 1662:9-1664:3, 1697:4-1698:4.) There was no evidence introduced that the inventions of the dependent claims of the '493 patent would have been obvious to a person of ordinary skill in the art at the time of their invention.

8. Commercial Embodiment of the Patented Inventions: ACULAR®

81. Syntex submitted an NDA to the FDA, pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act, seeking approval to market and sell a 0.5% ketorolac tromethamine ophthalmic solution, the drug that became ACULAR®. In 1992, the FDA approved ACULAR® for the treatment of ocular itch associated with seasonal allergic

conjunctivitis. In 1997, the FDA approved ACULAR® for use in the treatment of postoperative inflammation. (R.T. 1272:9-1274:15.)

82. ACULAR® is a sterile isotonic aqueous solution with a pH of 7.4. ACULAR® contains 0.5% wt/vol ketorolac tromethamine; 0.01% wt/vol BAC; 0.007% wt/vol Octoxynol 40; 0.1% wt/vol edetate disodium, a chelating agent; 0.79% wt/vol sodium chloride; hydrochloric acid and/or sodium hydroxide to adjust the pH; and purified water. ACULAR® includes each element of each of Claims 1-7 and 15-16 of the '493 patent, and the uses of ACULAR® include each element of each of Claims 8-14 of the '493 patent. Claim 7 of the '493 patent claims the ingredients of ACULAR® exactly, and Claim 14 of the '493 patent claims the use of ACULAR® exactly. (Trial Ex. 085; R.T. 1534:10-1536:14.)

83. In 1994, within one year of ACULAR®'s entry into the ophthalmic anti-inflammatory market, ACULAR®'s net sales were over $18 million. In 1995, ACULAR®'s net sales rose to over $21 million, and by 1999, its net sales had risen to over $46 million. In 2001, ACULAR®'s net sales were over $58 million. All told, during the period from ACULAR®'s introduction in 1993 through 2001, ACULAR® garnered over $291 million in net sales and captured a 36.1% market share among ophthalmic anti-inflammation drugs. (Trial Exs. 090,091; RT. 1541:13-1555:14,1558:23-1562:18.)

84. ACULAR® has consistently outperformed ACULAR PF®, a formulation of ACULAR® that contains the same previously-patented active

ingredient as ACULAR®, but does not contain BAC or Octoxynol 40. (Trial Exs. 092, 095, 096; R.T. 1566:5-12; id. at 1576:3-6.)

85. ACULAR® has also far outperformed its chief competitor drug, Voltaren Ophthalmic®, which appeared in the marketplace three years prior to ACULAR®. Voltaren Ophthalmic®, like ACULAR®, is an ophthalmic NSAID, but Voltaren Ophthalmic® contains a different active ingredient than the previously-patented ketorolac tromethamine contained in ACULAR®. Voltaren Ophthalmic® also does not contain Octoxynol 40. (Trial Exs. 091, 092, 095, 096; R.T. 1561:20-1562:18, 1577:8-14.)

86. Despite lagging behind ACULAR®, Voltaren Ophthalmic® has consistently far outperformed the only other drug containing the previously-patented active ingredient contained in ACULAR®, ACULAR PF®. (Trial Exs. 091, 092, 095, 096.)

87. Allergan entered into an exclusive distribution arrangement with Syntex for the 0.5% ketorolac tromethamine ophthalmic formulation on October 22, 1990, before the '493 patent issued. Allergan has paid to Syntex more than $133 million in royalties under this agreement. (Trial Exs. 083, 084; R.T. 1537:20-1540:24.)

88. Defendants ANDA 76-109 specifies that Defendants seek to market a drug that is identical to ACULAR® in its composition, preservative system, and intended uses. (Trial Ex. 058.)

9. Summary of Factual Findings

In sum, based on its review of the record evidence, including the '493 patent, the prior art references, and the testimony and exhibits presented at trial, and considering the directives that the Federal Circuit set forth in its remand order, the Court finds: (a) the prior art references do not suggest a motivation to combine; (b) Plaintiffs have shown that the inventions in the '493 patent produced unexpected results; and (c) Dr. Mitra's testimony does not establish that a motivation to combine existed.

B. Conclusions of law

1. Legal Standard - Obviousness

89. Section 103(a) of the Patent Act states that "[a] patent may not be obtained ... if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." *See KAO Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006).

90. "Because patents are presumed to be valid, *see* 35 U.S.C. § 282, an alleged infringer seeking to invalidate a patent on obviousness grounds must establish its obviousness by facts supported by clear and convincing evidence." *KAO Corp.*, 441 F.3d at 968 (citing *Apotex USA, Inc. v. Merck & Co.*, 254 F.3d 1031,1036 (Fed. Cir. 2001)).

91. Obviousness is a legal determination based on the following factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations, if any, of non-obviousness, such as commercial success, long-felt but unsolved need, failure of others, copying, and unexpected results. *See McNeil-PPC. Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1368 (Fed. Cir. 2003) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)).

92. The analysis under 35 U.S.C. § 103 "requires the oft-difficult but critical step of casting the mind back to the time of the invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999). Courts "cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1371 (Fed. Cir. 2000) (quoting *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988)). "[C]ase law makes clear that the best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references" *Id.* "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability-the essence of hindsight." *In re Dembiczak*, 175 F.3d 994 at 999.

93. Moreover, finding the elements of the patented invention in the prior art is simply the beginning of the analysis. The Federal Circuit cautions:

> As this court has stated, "virtually all [inventions] are combinations of old elements." Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability."

In re Rouffet, 149 F.3d 1350,1357 (Fed. Cir. 1998) (quoting *Envtl. Designs, Ltd. v. Union Oil Co.,* 713 F.2d 693, 698 (Fed. Cir. 1983) and *Sensonics, Inc. v. Aerosonic Corp.,* 81 F.3d 1566,1570 (Fed. Cir. 1996)) (citations omitted).

94. What is "[c]ritical to the analysis is an understanding of the particular results achieved by the new combination." *Gillette Co. v. S .C. Johnson & Son, Inc.,* 919 F.2d 720, 725 (Fed. Cir. 1990)

(quoting *Interconnect Planning Corp. v. Feil, 114* F.2d 1132, 1143 (Fed. Cir. 1985)). As the Federal Circuit held in *Gillette,* with respect to a chemical composition for a shaving gel: "There is no question that each component of [the patented] composition was separately known in the prior art. What was not known or suggested, however, was the composition that resulted from the combination of those components, and its unique properties." *Id.* at 724-725.

95. Defendants' burden of establishing obviousness in this case is particularly high because all of the prior art references asserted by Defendants at trial were before the examiner. *See Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.,* 796 F.2d 443,447 (Fed. Cir. 1986) ("[W]hen the prior art before the court is the same as that before the PTO, the burden on the party asserting invalidity is more difficult to meet.")

96. In general, however, the Court is not bound by the PTO's assessment of the prior art. *See Kingsdown Med. Consultants, Ltd, v. Hollister Inc.,* 863 F.2d 867, 872 (Fed. Cir. 1988) ("The district court is not, of course, bound by either the examiner's rejection in the parent application or the examiner's allowance in the continuation application."); *Lindemann Maschinenfabrik GMBH* v. *American Hoist and Derrick Co.* 730 F.2d 1452,1460 (Fed. Cir. 1984) ("Though the courts will give due respect to the examiner's evaluation of prior art, they are not of course bound thereby.") For example, the Court is not bound by the statement by the examiner that the inventions of the '493 patent

would have been obvious absent a showing of unexpected results. (SYN0000049.)

97. To prove obviousness, it is insufficient to demonstrate that the separate elements of the invention existed in the prior art. Rather, there must be some teaching or suggestion in the prior art to combine those elements, *see Arkie Lures, Inc. v. Gene Larew Tackle, Inc.,* 119 F.3d 953, 957 (Fed. Cir. 1997). "[A] showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential evidentiary component of an obviousness holding.'" *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.,* 229 F.3d 1120, 1124-25 (Fed. Cir. 2000) (quoting *C.R.. Bard, Inc. v. M3 Systems Inc.,* 157 F.3d 1340,1352 (Fed. Cir. 1998)). "[T]here must be some suggestion, motivation, or teaching in the prior art that would have led a person of ordinary skill in the art to select the references and combine them in a way that would produce the claimed invention." *Karsten Mfg. Corp. v. Cleveland Golf Corp.;* 242 F.3d 1376, 1385 (Fed. Cir. 2001). The showing of a suggestion, teaching or motivation to combine references "must be clear and particular." *In reDembiczak,* 175 F.3d at 999.

98. The burden of proving a motivation to combine is an element of the accused infringer's *prima facie* case that the patent is invalid for obviousness. *Tec Air, Inc. v. Denso Mfg. Michigan Inc.* 192 F.3d 1353, 1359-60 (Fed. Cir. 1999) ("To establish & *prima facie* case of obviousness, Denso must show some objective teaching in the prior art or that knowledge generally available to one of

ordinary skill in the art would lead that individual to combine the relevant teachings of the references.").

99. A patent challenger's burden to provide clear and convincing evidence of a motivation to combine the prior art references to arrive at the patented inventions is not lessened in the context of patents concerning chemical compounds. Rather, "[f]or a chemical compound, *a prima facie* case of obviousness requires 'structural similarity' between claimed and prior art subject matter... where the prior art gives reason or motivation to make the claimed compositions." *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacol, Inc.*, 231 F.3d 1339,1343 (Fed. Cir. 2000) (quoting *In re Dillon,* 919 F.2d 688, 692 (Fed. Cir. 1990)).

100. Furthermore, "an obviousness determination requires not only the existence of a motivation to combine elements from different prior art references, but also that a skilled artisan would have perceived a reasonable expectation of success in making the invention via that combination." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006).

2. The Inventions of the '493 Patent Produced Unexpected Results.

101. This Court previously concluded that the patented inventions produced unexpected results. (Doc. #350 at 153.) In its opinion remanding the case to this Court, the Federal Circuit directed this Court to reconsider that finding in light of the prosecution history and the testimony of Dr. Mitra. In particular,

the Federal Circuit directed this Court to reevaluate the criticisms by the first examiner of the data comparing Octoxynol 40, Tween 80, and Myrj 52 and to reconsider the fact that, during prosecution, the applicants did not submit Ms. Lidgate's results showing that "octoxynol 12.5 and Octoxynol 40 produced test samples that 'looked equivalent at all temperatures.'" *Syntex*, 407 F.3d at 382-83. The Federal Circuit also instructed this Court to consider Dr. Mitra's testimony regarding the substitutability of various surfactants in connection with the unexpected results inquiry. *Id.* at 1380-82.

102. As noted above, the examiner of Application No. 07/096,173 criticized the data comparing Octoxynol 40, Tween 80, and Myrj 52 for four reasons: (1) the data did not compare Octoxynol 40 to the surfactants of the primary references; (2) the concentration of Octoxynol 40 was greater than the concentrations of the other surfactants; (3) the data was not commensurate with the then-pending claims, which did not set proportions for the components of the formulations; and (4) the data was not in declaration form.

103. The data in the prosecution history showing that Octoxynol 40 outperformed Tween 80 and Myrj 52 is persuasive on the issue of unexpected results and is not rendered less so by any of the criticisms on the part of the examiner of the 07/096,173 application.

104. The Court has also considered Ms. Lidgate's test results regarding Octoxynol 12.5 and concludes that they do not undermine a conclusion that the

patented inventions did produced unexpected results. First, even if Octoxynol 12.5 were found to perform as well in the patented formulations as Octoxynol 40-an assumption that cannot be confirmed due to the absence of antimicrobial data regarding Octoxynol 12.5-this would not detract from the unexpected results demonstrated by the data comparing Octoxynol 40, Tween 80, and Myrj 52. In other words, it would still be unexpected to find that Octoxynol 40 outperformed these other well-known surfactants, and the record does not contain persuasive evidence establishing that other surfactants, such as Octoxynol 12.5, would have had the same result. Second, while Dr. Lidgate's test results allowed her to conclude that Octoxynol 12.5 and Octoxynol 40 were equivalent from a visual perspective, the data was too preliminary to allow her to make any further conclusions regarding their equivalence.

105. Defendants have argued that Ms. Lidgate's experiments that led to the submission of the Lidgate
Declaration improperly lacked a "control formulation"-that is, a formulation to which other formulations are compared. In fact, the formulation containing Octoxynol 40 was the formulation that other formulations were being compared against, and it therefore acted as the "control" formulation in the experiments. (R.T. 621:6-622:17.)

106. Dr. Mitra's testimony that a surfactant's possession of micelle-forming and non-ionic properties would necessarily lead that surfactant to have stabilizing abilities, and that therefore it was to

be expected that Octoxynol 40 would function "equally [as] well" as other micelle-forming, non-ionic surfactants in stabilizing ophthalmic formulations. R.T. at 1016:1-1018:15; id. at 1054:6-24; *id.* at 1122:14-1123:13; *id.* at 1129:3-16, fails on two levels to support a finding that Octoxynol 40's performance was not expected. First, if the state of knowledge at the time the inventions was that all micelle-forming, non-ionic surfactants would work "equally well," then Plaintiffs' evidence of the results of testing carried out by Ms. Lidgate-showing that Octoxynol 40 outperformed two other much more well-known micelle-forming, non-ionic surfactants-is highly unexpected. (R.T. 695:1-701:14; Trial Exs. 204, 205.) Moreover, the corollary to Dr. Mitra's substitutability theory, namely that Octoxynol 40 would be expected to function well as an ophthalmic formulation stabilizer, cannot be attributed to the state of the art at the time the '493 inventions were made. As noted above, neither the test results upon which Dr. Mitra based his conclusions, nor any similar test results, were known at the time of the patented inventions. The only data in evidence comparing the performance of Octoxynol 40 to surfactants disclosed in the prior art patents prior to the time of the patented inventions is the data from Ms. Lidgate's tests comparing the performance of Octoxynol 40 with the performance of Tween 80 and Myrj 52-other micelle-forming, non-ionic surfactants, which Dr. Mitra opined should perform "equally well." That data shows that Octoxynol 40 at a concentration of 0.004% outperforms Tween 80 and Myrj 50 at the significantly higher concentration of 0.01%. (Trial Ex. 24 at SYN0000280.)

107. In addition to the fact that Defendants' test results conducted years after the prosecution of the 493 patent are not relevant to the expectations of those skilled in the art at the time of the patented inventions, those results are also entitled only to limited weight due to the fact that a variety of grades, sources, or types of ingredients were not tested. Moreover, because the homolog content of the BAC used in a formulation has a significant effect on the degree of complexation between ketorolac tromethamine and BAC, Defendants cannot show that the results of their tests would have been the same had a different grade of BAC been used. Likewise, Defendants cannot show that the results of their tests would have been the same had a different source of ketorolac trometharaine been used. Finally, Defendants cannot show that the results of their tests would have been same had all carboxyl group-containing NSAIDs or all quaternary ammonium preservatives been tested.

108. Defendants further failed to establish that the ingredients used in their tests were substantially similar to the ingredients used by the Syntex researchers at the time of the application for the '493 patent. Therefore, the Court accords only limited weight to the results of tests that used ingredients that may have been different from those available at the time of the patent application.

109. Accordingly, the Defendants have failed to overcome the Plaintiffs' showing that the patented inventions produced unexpected results. This finding favors a conclusion that the inventions are non-obvious.

3. Motivation to Combine

110. In its prior order, the Court found that there could be no motivation to combine or modify the three prior art references asserted by Defendant-Waterbury, Gilbert, and Han-because those references teach away from the use of Octoxynol 40 in an ophthalmic formulation. (Doc. #350 at 141.) In its opinion remanding the case to this Court, the Federal Circuit directed the Court to reconsider whether Defendants have adduced clear and convincing evidence that there would have been a motivation to combine these references with the understanding that the references do not teach away from the use of Octoxynol 40. *Syntex,* 407 F.3d at 13 80. Accordingly, the Court will reassess the facts presented above to determine whether Defendants have proven that there would have been a motivation to combine or modify the prior art to arrive at the patented inventions notwithstanding the fact that Waterbury, Gilbert, and Han do not teach away.

111. The Court finds that a person of ordinary skill in the art at the time of the inventions of the '493 patent would not have had a motivation to combine the Waterbury, Gilbert, or Han patents with the *McCutcheon 's* reference. The Court also finds that a person of ordinary skill in the art at the time of the inventions of the '493 patent would not have had a reasonable expectation of success from doing so. Plaintiffs' expert, Dr. Stella, testified that there was nothing in *McCutcheon 's* that would have motivated one of ordinary skill in the art to combine it with the

other prior art references to arrive at the patented inventions. Defendants offered no evidence or testimony regarding *McCutcheon's*. Moreover, because *McCutcheon's* discloses the use of Octoxynol 40 only in the context of mixing non-water-miscible materials with water, *McCutcheon's* fails to provide any expectation that Octoxynol 40 could be successfully used to stabilize solutions that do not contain an oil-based component. There is nothing in *McCutcheon's* that provides any expectation that Octoxynol 40 could successfully stabilize the interaction of an NSA1D and a preservative or that Octoxynol 40 could safely be used in an ophthalmic formulation.

112. Nor is there any motivation to modify the teachings of the Waterbury, Gilbert or Han patents to substitute Octoxynol 40 for the surfactants disclosed in those references. There is nothing in these patents that suggests that one should search for a substitute surfactant, or that discloses a functional equivalency between Octoxynol 40 and other water-soluble, micelle-forming, non-ionic surfactants-or among all surfactants possessing these properties. Defendants improperly argue that the only "difference" between the inventions of the '493 patent and the prior art-Octoxynol 40-would have been suggested by prior art references disclosing other surfactants such as the Polysorbate 80 "disclosed" in the Waterbury patent. This focus on the "difference" between the patented invention and the prior art is a legally improper use of hindsight:

> What we stressed in *Kimberly-Clark*, and have repeated many times since,

> was that 35 U.S.C. § 103 requires analysis of a claimed invention as a whole.
>
> It is true that [the claimed invention] consists of a combination of old elements so arranged as to perform certain related functions. It is immaterial to the issue, however, that all of the elements were old in other contexts. What must be found obvious to defeat the patent is the claimed combination. Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness.

Gillette, 919 F.2d at 724 (quoting *Kimberly-Clark Corp, v. Johnson & Johnson,* 745 F.2d 1437, 1448 (Fed. Cir. 1984)) (citation omitted). Defendants' focus on Octoxynol 40 as an obvious "substitution" for, *e.g.*, Polysorbate 80, violates this fundamental tenet of the obviousness analysis.

113. This type of hindsight focus is no more permissible in the context of chemical compounds than it is elsewhere, *see Yamanouchi,* 231 F.3d at 1345 (stating that "this case has all the earmarks of somebody looking at this from hindsight"), unless the prior art references disclose "functional equivalencies" between the compound used in the invention and a compound found in the prior art, or the patent challenger proves by clear and convincing evidence that those of ordinary skill in the art at the

time of the patented inventions expected such functional equivalencies. *See In re Mayne,* 104 F.3d 1339, 1343 (Fed. Cir. 1997); *In re Dillon,* 919 F.2d at 692; *cf. Rhone Poulenc Agro, S.A. v. DeKalb Genetics Corp.,* 272 F.3d 1335, 1357 (Fed. Cir. 2001) ("In order to draw the *Dillon* analogy, DeKalb must demonstrate that in the relevant field of art, plant molecular biology, it was expected that constructs imparting glyphosate tolerance would have similar properties with and without a second transit peptide. DeKalb points to no evidence that demonstrates any expectation in the relevant field of art [.]"). Because Defendants have pointed to no expectations of-or prior art references disclosing-functional equivalency between Octoxynol 40 and any surfactant disclosed in the Waterbury, Gilbert or Han patents, Defendants' focus on the substitutability of Octoxynol 40 for these prior art surfactants remains an improper use of hindsight.

114. Dr. Mitra's theory-presented at trial-that all water-soluble, non-ionic surfactants should work equally well in stabilizing solutions consisting of NSAIDs and quaternary ammonium preservatives provides no support for Defendants' argument that it would have been obvious to one of ordinary skill in the art at the time of the patented inventions to substitute Octoxynol 40 for any of the surfactants disclosed in the prior art patents. Defendants adduced no evidence that anyone at the time of the patented inventions shared Dr. Mitra's opinion, in fact, the "Surfactant Systems" treatise, from 1983, showed that all water-soluble, micelle-forming, non-ionic surfactants do not perform alike. (Trial Ex. 033

at 343-44.) In order to prove motivation to modify by substitution of chemical equivalents, a patent challenger must demonstrate that in the relevant field of art at the time of the patented inventions, it was expected that different chemical compounds would have relevantly similar properties. *Rhone Poulenc,* 272 F.3d at 1357.

115. Nor did Defendants adduce any evidence that the data from any experiments similar to those offered by Defendants to support Dr. Mitra's substitutability assertions was known at the time of the patented inventions. Absent such a showing, these experiments (and Dr. Mitra's conclusory statement that all non-ionic surfactants are equally effective) are not persuasive to the question of whether there would have been a motivation to combine at the time of the patented inventions. *Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367,1380 n.4 (Fed. Cir. 1986) (rejecting reliance on evidence dated after the filing date of the patent because "obviousness must be determined as of the time the invention was made"); *Richardson-Vicks Inc. v. Upjohn Co.,* 122 F.3d 1476, 1480 (Fed. Cir. 1997) ("The obviousness of a patent claim is determined 'at the time the invention was made.' 35 U.S.C. § 103.").

116. Defendants' reliance on Dr. Mitra's hindsight reasoning, in combination with Dr. Stella's testimony that there was no motivation to combine, *see* R.T. at 1715:17-22, constitutes substantial evidence to defeat Defendants' obviousness claim. "Expert testimony of a 'lack of motivation to combine and the use of hindsight by [opposing experts]

constitutes substantial evidence of nonobviousness.'" *Group One, Ltd. v. Hallmark Cards, Inc.*, 407 F.3d 1297, 1304 (Fed. Cir. 2005) (brackets in original) (quoting *Teleflex, Inc., v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1334 (Fed. Cir. 2002)).

117. Accordingly, Defendants have failed to prove, by clear and convincing evidence, that there would have been a motivation to combine or modify the asserted prior art references to arrive at the patented inventions. As a result, Defendants have failed to make out *a prima facie* case that the '493 patent is invalid for obviousness.

4. Objective Evidence Relating to Obviousness

118. Because Defendants have failed to prove the *prima facie* element of a motivation to combine, they have failed to prove the '493 patent invalid for obviousness. *See Tec Air*, 192 F.3d at 1359-60; *see also Alza Corp. v. Mylan Labs., Inc.*, 391 F.3d 1365, 1373 n.9 (Fed. Cir. 2004) ("Because Mylan has not made a prima facie case of obviousness, we need not address the parties' assertions regarding the district court's discussion of secondary considerations.").

119. Furthermore, Plaintiffs introduced objective evidence that strongly attests to the non-obviousness of the inventions of the '493 patent. In this regard, the Court has considered the objective evidence of non-obviousness, such as, for example, commercial success and industry acclaim, licensing and royalty payments, unsuccessful attempts to create the invention, long-felt need, and unexpected results.

See Apple Computer, Inc. v. Articulate Systems, Inc., 234 F.3d 14, 26 (Fed. Cir. 2000); *Ecolochem, Inc. v. S. Cal Edison Co,,* 227 F.3d 1361,1376-80 (Fed Cir. 2000); *John Charles Designs, Inc. v. Queen Int'l Design, Inc., Inc.*, 940 F. Supp. 1516,*1521* (C.D. Cal. 1996). As the Federal Circuit has noted, "evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decision maker remains in doubt after reviewing the art." *Stratoflex, Inc.* v. *Aeroquip Corp.*, 713 F.2d 1530,1538-39 (Fed. Cir. 1983). In many cases, such as in this case, the objective evidence of non-obviousness, which must be considered by the Court, includes facts that arise after the issuance of the patent and that therefore could not have been considered by the patent examiner.

5. Commercial Success of ACULAR®

120. Plaintiffs have submitted copious evidence that their commercial embodiment of the patented inventions, ACULAR®, has had commercial success. See 71-74, supra.

121. A nexus between the patented inventions and commercial success is presumed to exist when the features of the patented drug are embodied in a commercially marketed product. As the Federal Circuit held in *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120,1130 (Fed. Cir. 2000), "[a] nexus between commercial success and

the claimed features is required. However, if the marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus." (emphasis added, citations omitted).

122. The Court previously found that the commercial success of ACULAR© favored a finding of non-obviousness in this case. See Findings of Fact and Conclusions of Law of Dec. 29,2003 at 146-49. In its opinion remanding the case to this Court, the Federal Circuit directed the Court to reconsider that finding in light of its opinion in *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364,1376-77 (Fed. Cir. 2005). In Merck, the Federal Circuit held that a patent challenger may disprove the presumed nexus between commercial success and the patented inventions by showing that the commercial success of the marketed product derived more from the fact that it contains a separately patented active ingredient than from the other features of the patent that the product as a whole embodies. Id. Here, the record evidence shows that ACULARO®'s commercial success derives from its embodiment of the entire combination taught by the '493 patent, and not from the fact that its active ingredient, ketorolac tromethamine, was previously protected by another patent. This conclusion is apparent from the facts that, in terms of sales and market share, (a) ACULAR® has consistently outperformed ACULAR PF®, a formulation of ACULAR® that contains the same active ingredient as ACULAR®, but does not contain BAC or Octoxynol 40, and (b) Voltaren

Ophthalmic®, a competing ophthalmic NSAID that contains a different active ingredient from ACULAR® and ACULAR PF®, and that also does not contain BAC or Octoxynol 40, has also far outperformed ACULAR PF®, despite (c) lagging behind ACULAR®. R.T. 1565:1-7; *id.* at 1567:5-12; *id.* at 1579:3-18; *id.* at 1578:8-16; Trial Exs. 091, 092, 095, 096.

123. Accordingly, the Court finds that the commercial success of ACULAR® favors a finding of non-obviousness.

6. Evidence of Third Party Licensing

124. The non-obviousness of the '493 patent is further demonstrated by the fact that a third party (Allergan) entered into an exclusive distribution agreement with Syntex before the '493 patent was issued and has paid Syntex over $133 million in royalties under that agreement. *See Arkie Lures,* 119 F.3d at 957 (noting that licensing activity "may be highly probative of the issue of nonobviousness"). As with the evidence of commercial success, this "highly probative" evidence of royalty payments could not have been considered by the patent examiner because it had not yet occurred.

7. Inventions Satisfied a Long-Felt Need

125. The fact that the inventions satisfied a long-felt need present at Syntex for a ketorolac-based ophthalmic drug also weighs strongly in favor of a finding of non-obviousness. *See Hewlett-Packard Co. v. Tel-Design, Inc.*, 460 F.2d 625,631 (9th Cir. 1972) ("The evidence of prior unsuccessful attempts to solve the same problem established both the pressing need for such a solution as well as the fact that the solution had not been obvious to those whom the court found to be highly skilled in the pertinent art."). As stated by the Federal Circuit in a similar case:

> Pratt's extensive efforts to solve the problem of isolating the weighing system indicate the absence of a suggestion to combine the Brewster machine with the positive intermixing, elements of the volume machines. These efforts by Pratt tend to show that one skilled in the art would have had no reasonable expectation of success in combining the prior art machines in question. Long-felt need in the face of prior art later asserted to lead to a solution tends to negate the proposition that the combination of such prior art would have been obvious.

Micro Chem., Inc. v. Great Plains Chemical Co., Inc., 103 F.3d 1538,1547 (Fed Cir. 1997) (citations omitted), abrogated on other grounds by *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55 (1998). The fact that Syntex scientists tried unsuccessfully for several years to formulate a ketorolac tromethamine

ophthalmic solution using other surfactants and ingredients suggests that the inventions of the patent were not obvious.

126. On remand, Defendants argue that unsuccessful attempts to solve the problems addressed by the patent in suit are only relevant if they are unsuccessful attempts by scientists other than the inventors of the patent in suit. This argument fails, because in this case, the unsuccessful attempts were by scientists other than Dr. Fu and Ms. Lidgate (the inventors of the '493 patent), such as Ms. Pulsipher. In any event, the Federal Circuit has frequently focused on the unsuccessful attempts of the patentee in its obviousness analyses. *See, e.g., Micro Chem., Inc.*, 103 F.3d at 1547 (holding that the patent-in-suit, invented by William C. Pratt, was non-obvious and reasoning that "Pratt's extensive efforts to solve the problem of isolating the weighing system indicate the absence of a suggestion to combine the Brewster machine with the positive intermixing elements of the volume machines"); *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) (holding that "the five to six years of research [by the patentee] that preceded the claimed invention" supported the conclusion that "[t]he evidence as a whole does not support the PTO's conclusion that the claimed invention would have been obvious in terms of 35 U.S.C. § 103").

127. In short, all of these secondary considerations favor a finding of non-obviousness.

8. Validity of Dependent Claims

128. "Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of the other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim." 35 U.S.C. § 282.

129. On remand, Defendants raised for the first time the argument, based on dicta from *Dayco Products, Inc. v. Total Containment, Inc.*, 329 F.3d 1358,1370-71 (Fed. Cir. 2003), that they need not prove invalidity as to each claim of the '493 patent because the issues of validity to be resolved as to each claim are "substantially materially identical." Defendants, however, made no attempt to analyze or compare the dependent and independent claims of the '493 patent in an attempt to prove that the issues affecting the claims are "substantially materially identical." Given that the dependent claims of the '493 patent disclose more detailed inventions than the patent's independent claims, and that the elements claimed in the dependent claims have a major effect on the stability and antimicrobial effectiveness of the formulations, Defendants cannot meet their burden of proving the invalidity of these claims by clear and convincing evidence by simply stating, in conclusory fashion, that the dependent claims are "mere optimizations or preferred embodiments" of the independent claims. (DRB at 13-14.)

130. Because there was no evidence introduced that the more detailed inventions of the dependent

claims of the '493 patent would have been obvious to a person of ordinary skill in the art at the time of their invention, the Court finds that the inventions of the dependent claims (Claims 2-7, 9-14, and 16) would not have been obvious to such a person.

III. Conclusion as to Obviousness Challenge and Request for Injunctive Relief

131. As established by the findings of fact set forth above, Defendants have failed to prove that there would have been a motivation to combine or modify the prior art references to arrive at the patented inventions. Moreover, each of the secondary considerations favors a finding that the '493 patent is not invalid for obviousness. Accordingly, the Court concludes that the Defendants have failed to prove by clear and convincing evidence that any claim of the '493 patent is invalid under 35 U.S.C. § 103.

132. Section 271(e)(4) provides, in relevant part:

For an act of infringement described in [35 U.S.C. § 271(e)(2)]:

> (A) the court shall order the effective date of any approval of the drug [] involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed,
>
> (B) injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, offer to

> sell, or sale within the United States or importation into the United States of an approved drug[.]

Because this Court has found that the filing of Defendants' ANDA infringed each claim of the '493 patent, and because Defendants have not proven that any of those sixteen infringed claims is invalid or unenforceable, the Court orders as follows: (1) that the effective date of any approval of Defendants' ANDA under § 505(j) of the Federal Food, Drug & Cosmetic Act (21 U.S.C. § 355(j)) for the drug product "Ketorolac Tromethamine Ophthalmic Solution 0.5%" be a date not earlier than the expiration date of the '493 patent; (2) that Defendants, and all persons and entities acting in concert with Defendants, be enjoined from making, using, selling, or offering for sale in the United States, or importing into the United States, any products that infringe, induce the infringement of, or contributorily infringe the '493 patent; and (3) that Defendants, and all persons and entities acting in concert with Defendants, be enjoined from making preparations to make, use, sell, or offer for sale Ketorolac Tromethamine Ophthalmic Solution 0.5% in the United States.

IT IS SO ORDERED.

Dated: June 2,2006.

/s/ Martin J. Jenkins
MARTIN J. JENKINS
UNITED STATES
DISTRICT JUDGE

United States Court of Appeals for the Federal Circuit

04-1252

SYNTEX (U.S.A.) LLC and ALLERGAN, INC.,

Plaintiffs-Appellees,

v.

APOTEX, INC., APOTEX CORP., and NOVEX PHARMA,

Defendants-Appellants.

David J. Harth, Heller Ehrman White & McAuliffe LLP, of Madison, Wisconsin, argued for plaintiffs-appellees. With him on the brief were Alexander L. Brainerd, Keith R. Weed, and Olga Rodstein. of Menlo Park, California, and Christine Saunders Haskett. of San Francisco, California.

Manny D. Pokotilow. Caesar, Rivise, Bernstein, Cohen & Pokotilow, LTD., of Philadelphia, Pennsylvania, argued for defendants-appellants. With him on the brief were Robert S. Silver. Alan H. Bernstein. Mona Gupta and William J. Castillo. Of counsel on the brief was Ronald S. Lemieux. Squire, Sanders & Dempsey L.L.P., of Palo Alto, California.

Appealed from: United States District Court for the Northern District of California

Judge Martin J. Jenkins.

United States Court of Appeals for the Federal Circuit

04-1252

SYNTEX (U.S.A.) LLC and ALLERGAN, INC.,

Plaintiffs-Appellees,

v.

APOTEX, INC., APOTEX CORP., and NOVEX PHARMA,

Defendants-Appellants.

DECIDED: May 18, 2005

Before CLEVENGER. GAJARSA. and PROST. Circuit Judges.

Opinion for the court filed by Circuit Judge GAJARSA. Concurring opinion filed by Circuit Judge PROST.

GAJARSA. Circuit Judge.

Apotex, Inc., Apotex Corp. and Novex Pharma (collectively "Apotex") appeal from the final judgment of the United States District Court for

the Northern District of California, which, after a bench trial, held U.S. Patent No. 5,110,493 (the "'493 patent") owned by Syntex (U.S.A.) LLC not invalid, enforceable, and infringed by Apotex's Abbreviated New Drug Application ("ANDA"). Allergan, Inc., Syntex's distributor, has exclusive rights to manufacture the commercial embodiment of the '493 patent marketed under the trademark ACULAR.[1] Syntex (U.S.A.) LLC v. Apotex, Inc., No. 01-CV-2214 (January 27, 2004). Because we find the district court committed legal error in establishing certain factual predicates to its non-obviousness determination, we reverse the judgment of validity and remand for further consideration consistent with this opinion.

BACKGROUND

A. The Patents and Prosecution History

The '493 patent, entitled "Ophthalmic NSAID Formulations Containing a Quaternary Ammonium Preservative and a Nonionic Surfactant," claims a formulation for sterile, preserved eye drops to treat eye inflammation such as that caused by conjunctivitis or eye surgery.

The '493 patent teaches combining a nonsteroidal anti-inflammatory drug ("NSAID") such as ketoralac tromethamine ("KT") and a quaternary ammonium preservative such as benzalkonium chloride ("BAC") with a surfactant

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[1] Hereinafter, the appellees are collectively referred to as "Syntex." ACULAR is a trademark owned by Syntex, Inc.

such as octoxynol 40. The NSAID is the active ingredient for reducing eye inflammation. The quaternary ammonium preservative, in turn, kills any bacteria introduced into the eye during administration of the NSAID. However, quaternary ammonium preservatives, such as BAC, do not always mix well with NSAIDs. Neither ingredient is water soluble, and the two active ingredients may react with each other to form complexes when mixed. These complexes will eventually cause the mixture to look cloudy or lose its antibacterial properties.

The chemical arts often solve this type of mixing problem by using surfactants. A surfactant is a "surface active agent" used to make otherwise insoluble chemicals soluble in water. The '493 patent claims to solve the complex formation problem by adding octoxynol 40, a surfactant, to the KT/BAC mixture.

The '493 patent claims ophthalmic formulations (eye drops) useful for treating eye inflammation, methods of using eye drops to treat eye disease, and preservative systems for use in eye drops. The claims of the '493 patent fall into three categories: claims 1 to 7 are composition claims, claims 8 to 14 are method claims, and claims 15 and 16 recite a "preservative system." Claims 1, 8, and 15 are independent claims, the others are all dependent. Claim 1, the basic embodiment of the compound, provides:

1. An ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation, comprising:

an opthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug in an effective amount for ophthalmic treatment between 0.001% and 10.0% wt/vol;

a quaternary ammonium preservative in an antimicrobially effective amount between 0.0001% and 1.0% wt/vol;

an ethoxylated alkyl phenol that conforms generally to the formula $C_8Hi7C_6H4(OCH2CH2)nOH$[2] where n has an average value of 40 in a stabilizing amount between 0.001% and 1.0% wt/vol; and an aqueous vehicle q.s. to 100%.

"493 patent, col. 8, II. 42-55.

The "493 patent issued from U.S. Patent Application No. 07/624,027 ("the "027 application"), which was filed on December 7, 1990. The '027 application was a continuation of U.S. Patent Application No. 07/096,173 ("the '173 application") filed on September 11, 1987. The two applications were reviewed by different examiners at the Patent and Trademark Office ("PTO").

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[2] This is the formula for octoxynol 40.

Each examiner rejected the application before him as obvious in view of U.S. Patent No. 4,349,563 to Gilbert and U.S. Patent No. 4,559,343 to Han in view Of McCutcheon's Emulsifiers and Detergents p.154 (1982) ("McCutcheon's"). U.S. Patent No. 4,454,151 to Waterbury, another patent assigned to Syntex, was listed on the '493 patent as prior art, but was not cited by the examiner in his obviousness rejection. The prior art patents Waterbury, Gilbert, and Han all teach ophthalmic formulations containing NSAIDs, quaternary preservatives, and nonionic surfactants to stabilize the formulation. While Waterbury, Gilbert, and Han do not teach the specific use of octoxynol 40, they do teach using the general class of water-soluble nonionic surfactants as stabilizers. Waterbury and Gilbert teach the use of polysorbate 80.[3] McCutcheon's, a comprehensive directory of emulsifiers and detergents, teach that octoxynol 40 was a known stabilizer. According to both examiners, it was well known in the art that surfactants such as octoxynol 40 have a stabilizing effect on ophthalmic compounds containing NSAIDs.[4] The examiner reviewing the '027 continuation application rejected what has become claim 1 on the grounds that "[t]he

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[3] Polysorbate 80 is sometimes referred to as "tween 80" by the PTO, district court, and the parties. For the purposes of this opinion, all references to tween have been replaced with polysorbate 80.

[4] Consequently, within the context of this art, surfactants are sometimes referred to as stabilizers.

mere substitution of one [surfactant] for another... is not deemed a patentable distinction in the absence of a showing of some unobvious result."

Syntex responded to that rejection by asserting that it had provided acceptable data demonstrating results superior to the formulations disclosed by the Han and Gilbert references. Syntex supported its superior results claim with a declaration from Deborah M. Lidgate ("Lidgate"), one of the named inventors. In the declaration, Lidgate stated that "octoxynol 40, and not octoxynol 3 or octoxynol 5, is suitable to use with benzalkonium chloride to prepare a preservative system for an ophthalmic formulation, or to prepare an ophthalmic formulation, of the present application." In presenting her findings of superior results, Lidgate excluded the additional experimental data that she had developed showing octoxynol 12.5 to be a surfactant capable of stabilizing a KT/BAC formulation.

Following this submission, the examiner allowed the application to issue, stating that Syntex had "overcome the prior art rejections... by showing that unexpected results are obtained when one uses [octoxynol 40]. These results are unobvious because one of ordinary skill in the art would not have known that one surfactant would outperform other surfactants." The patent issued on May 5,1992.

Syntex markets the patented ophthalmic formulation as ACULAR. ACULAR embodies the claims of the '493 patent and has been approved by

the Food and Drug Administration ("FDA"). From 1993 to 2001, ACULAR captured a substantial market share for ophthalmic anti-inflammation drugs.

B. The Hatch-Waxman Amendments

The Hatch-Waxman Amendments[5] to the Federal Food, Drug, and Cosmetic Act permit an applicant to file an ANDA with the FDA requesting approval of a bioequivalent ("generic") version of a drug that is already listed by the FDA as approved for safety and effectiveness without having to submit additional safety and efficacy data. See 21 U.S.C. § 355(j)(2)(A). The overall scheme of the Hatch-Waxman Amendments is described in detail in our decisions in Mylan Pharmaceuticals. Inc. v. Thompson, 268 F.3d 1323 (Fed. Cir. 2001) and Andrx Pharmaceuticals. Inc. v. Biovail Corp., 276 F.3d 1368 (Fed. Cir. 2002) and need not be repeated here. For the purposes of this opinion it suffices to know that an ANDA may be filed for drugs currently protected by patents and listed in the FDA's Orange Book. Mylan Pharmaceuticals. Inc., 268 F.3d at 1325-26. In its filing, the applicant must certify either (1) that it will not market its drug prior to the expiration of the relevant patents, or (2) that the relevant patents "are invalid or will not be infringed by the manufacture, use or sale of the new drug for which the ANDA is submitted." 21

[5] The Hatch-Waxman Amendments were enacted as a part of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, codified at 21 U.S.C. §§ 355 and 360cc, and 35 U.S.C. §§ 156, 271, 282.

U.S.C. § 355(j)(2)(A)(vii)(IV). An ANDA applicant filing its application with the FDA and making a Section IV certification must notify the holder of the patent, who may then bring an action against the applicant for infringement under 35 U.S.C. § 271(e)(2). See 21 U.S.C. §§ 355(j)(2)(B)(i) and (j)(5)(B)(iii). In its notice the applicant must include "a detailed statement of the factual and legal basis [sic] of the opinion of the applicant that the patent is invalid or will not be infringed." 21 U.S.C. § 355(j)(2)(B)(iv). Such a notice can state that the patent is invalid on the basis of anticipation, obviousness or non-enforceable for patent misuse or inequitable conduct. Submission of an ANDA is an act of patent infringement if the ANDA seeks approval to manufacture, use, or sell a drug that is claimed in a patent or the use of which is claimed in a patent. 35 U.S.C. § 271 (e);[6]

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[6] 35 U.S.C. § 271 (e) provides in relevant part:

> (2) It shall be an act of infringement to submit-
> (A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent, ... if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug or veterinary biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

An ANDA is an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act.

Eli Lilly & Co. v. Medtronic. Inc., 496 U.S. 661, 676 (1990) ("The function of [35 U.S.C. § 271 (e) is] to define a new (and somewhat artificial) act of infringement for a very limited and technical purpose that relates only to certain drug applications.").

C. The District Court Proceedings

Apotex manufactures generic Pharmaceuticals. On April 25, 2001, Apotex notified Syntex that it had filed ANDA 76-109 with the FDA to market a generic version of ACULAR including a Section IV certification. In its notice to Syntex, Apotex stated that it believed the '493 patent to be invalid on the grounds of obviousness and inequitable conduct, and not infringed by Apotex's proposed generic version of ACULAR. On June 6, 2001, Syntex filed suit against Apotex for patent infringement.

The district court held a Markman hearing and issued a Claim Construction Order. In construing two disputed claim terms[7] of the '493 patent, the district court ruled that the term "in a stabilizing amount" in claim 1 was not a limitation, but merely described the intended results of using octoxynol 40 in an "amount between 0.001% and 1.0% wt/vol." '493 patent, col. .8, line 55. The claim term makes clear that

[7] The district court's conclusion that the claim term "antimicrobially effective" is not a claim limitation is not being appealed.

combining the recited ingredients in the claimed weight to volume ratio will stabilize the compound.

Syntex moved for summary judgment of infringement based upon the court's specific claim construction. Apotex did not oppose Syntex's motion. The district court compared the claims of the '493 patent with the drug formulation and uses set forth in Apotex's ANDA 76-109 application and determined that there was no factual dispute. The district court found that the generic version of ACULAR identified in the ANDA 76-109 submission would infringe each claim of the '493 patent, and granted Syntex's motion for partial summary judgment that Apotex had literally infringed each claim of the '493 patent.

After a bench trial on the issues of invalidity and unenforceable, the district court restated its determination that Apotex's proposed generic version of ACULAR infringed all of the claims of the '493 patent. The district court found that ACULAR is coextensive with the method claims of the '493 patent. The district court also determined that Apotex's proposed generic drug is virtually identical to ACULAR in its composition, preservative system, and intended uses. On the basis of these findings, the district court reiterated that the formulation defined by ANDA 76-109 directly infringed claims 1-6, 8-13, and 15-16 of the '493 patent. The district court further

stated that claims 7 and 14 were infringed under the doctrine of equivalents.[8]

The district court held that the '493 patent was not invalid, rejecting Apotex's invalidity arguments based on obviousness. Moreover, the district court concluded that Syntex had overcome the PTO examiner's obviousness objection by making a showing that the prior art taught away from the use of octoxynol 40 in ophthalmic solutions containing BAC and NSAIDs, and that the use of octoxynol 40 generated unexpected results. The district court also found that the substantial success of ACULAR on the market confirmed that the '493 patent claims were non-obvious. Finally, the district court found no inequitable conduct. The court rejected Apotex's contentions that Syntex had affirmatively misrepresented the unexpected nature of octoxynol 40's ability to stabilize the KT/BAC combination by deliberately withholding test results concerning the ability of octoxynol 12.5 to accomplish the same objectives as the claimed surfactant. The district court found that the test results concerning octoxynol 12.5 were not material, and that Syntex lacked intent to deceive the PTO.

Apotex appeals the district court's claim construction ruling, its judgment of infringement,

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[8] Claims 7 and 14, the district court observed, specified a sodium chloride concentration of 0.79%. The ANDA formulation contains 0.8% sodium chloride. The court concluded this minor difference would not permit the ANDA formulation to escape infringement under the doctrine of equivalents.

its non-obviousness determination, and its finding of no inequitable conduct. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

A. Standard of Review

This court reviews de novo the grant of summary judgment. Genzyme Corp. v. Transkaryotic Therapies, Inc., 346 F.3d 1094, 1096 (Fed. Cir. 2003). Summary judgment is appropriate when there are no genuine issues of material fact and the moving party is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(c); Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 247-48 (1986). A determination of patent infringement consists of two steps: (1) the court must first interpret the claim, and (2) it must then compare the properly construed claims to the allegedly infringing device. See Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1454 (Fed. Cir. 1998) (en banc). Claim construction, the first step, is a matter of law that this court reviews de novo. Id. at 1456. Generally, the second step is a factual question that we review for clear error. Bai v. L & L Wings, Inc., 160 F.3d 1350, 1353 (Fed. Cir. 1998). However, factual inferences that are material to the grant of a summary judgment are not accorded such deference—they are reviewed to ascertain whether there is a genuine issue of material fact. Lemelson v. TRW, Inc., 760 F.2d 1254, 1260 (Fed. Cir. 1985).

This court reviews for clear error the district court's determination of the factual inquiries

underlying obviousness, while it reviews de novo the legal conclusion that a claim is invalid as obvious. McNeil-PPC. Inc. v. L Perriqo Co., 337 F.3d 1362, 1368 (Fed. Cir. 2003), cert, denied, 540 U.S. 1107 (2004). The factual determinations relevant to the obviousness inquiry include: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations, if any, such as commercial success, unexpected results, copying, long-felt but unresolved need, and the failure of others to develop the invention. Graham v. John Deere Co., 282 U.S. 1, 17-18 (1966). "What the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references are questions of fact." In re Fulton, 391 F.3d 1195,1199-1200 (Fed. Cir. 2004).

A finding of inequitable conduct is committed to the trial judge's discretion and is reviewed under an abuse of discretion standard. Kinasdown Med. Consultants, Ltd. v. Hollister. Inc., 863 F.2d 867, 876 (Fed. Cir. 1988). 'To overturn such a determination, the appellant must establish that the ruling is based on clearly erroneous findings of fact or on a misapplication or misinterpretation of applicable law, or evidences a clear error of judgment on the part of the district court." Molins PLC v. Textron. Inc., 48 F.3d 1172, 1178 (Fed. Cir. 1995) (citing Kinqsdown Medical Consultants. 863 F.2d at 876. Findings of materiality and intent are factual findings subject to the clearly erroneous standard and, therefore, will not be disturbed on

appeal unless this court has a definite and firm conviction that a mistake has been committed. Id.

B. Claim Construction

Apotex challenges the district court's claim construction on the ground that the term "in a stabilizing amount" should properly be read as a claim limitation. We agree with the district court that the term "in a stabilizing amount" simply describes the intended result of using the weight to volume ratios recited in the claims. Accordingly, we conclude that the district court correctly construed the disputed term of the '493 patent and correctly determined that Apotex's proposed generic version of ACULAR would infringe all of the claims of the '493 patent. We now turn to Apotex's assertions of invalidity and unenforceability.

C. Obviousness

On appeal, the critical issue is whether the use of the surfactant octoxynol 40 in the claimed formulations is an obvious alteration of similar formulations taught in the prior art. Because the district court clearly erred in its fact findings regarding obviousness, we remand for further consideration.

At trial, Apotex argued that based on the prior art, a person of ordinary skill in the art would expect to succeed in stabilizing a formulation containing an NSAID and BAC with a nonionic surfactant.

Contending that the formulation claimed in the '493 patent is just such a formulation, Apotex argued that it is legally obvious.

After conducting a bench trial, the district court made factual findings pertaining to the issue of obviousness. The district court noted that because the prior art at issue had been before the examiner during prosecution, the burden of proving the challenged claims obvious "is particularly high." Syntex (U.S.A.) LLC v. Apotex, Inc., No. 01-CV-2214, slip op. at 40, (Dec. 29, 2003). The trial court then concluded that Apotex had failed to meet this heightened burden. In particular, the court held that nonobviousness was demonstrated by the fact that octoxynol 40 had never been used in a drug formulation; there was no motivation to combine the prior art references, which teach away from the use of the surfactant octoxynol 40; that the use of octoxynol 40 in the claimed formulation produced unexpected results; and that Syntex had provided convincing evidence of the commercial success of ACULAR, the product purportedly covered by claims of the '493 patent. Syntex, slip op. at 45.

Our review of the record reveals clear error by the district court in several of the grounds that led it to conclude that the invention claimed by the claims in suit would not have been obvious. First, the court clearly erred in finding that "[n]o pharmaceutical formulation other than ACULAR has ever included Octoxynol 40." Second, the court clearly erred in discussing the McCutcheon reference and in finding that each of the Waterbury, Gilbert, and Han references teach away

from the use of octoxynol 40 in the claimed formulations. Further, the court was under the impression that, in the absence of evidence that those references teach away from combination, there was a failure of proof that there would have been any motivation by one of ordinary skill in the art to use octoxynol 40 in the claimed formulations. In so concluding, the district court failed to examine the expert testimony of Dr. Mitra on the question of whether one of ordinary skill in the art would have deemed the invention obvious, and as a subset of the overall obviousness question, whether octoxynol 40 produced the unexpected results asserted by Syntex. In addition, we think the district court failed to appreciate that the prosecution history of the relevant patents, while not establishing inequitable conduct, casts some doubt on the final examiner's conclusion that the claimed surfactant produces unexpected results sufficient to overcome a prima facie case of obviousness. Finally, we feel the district court should reconsider the significance of the commercial success of the patented formulation in light of our recent decision in Merck & Co. v. Teva Pharmaceuticals. USA, Inc., 395 F.3d 1364 (Fed. Cir. 2005).

On remand, the district court's reconsideration of the obviousness issue should proceed in light of our corrections of the record.

1. Use of Octoxynol 40 in Pharmaceuticals

The district court erred in finding that octoxynol 40 was not used in Pharmaceuticals

prior to its use in the patented invention. This finding is clearly contradicted by statements in the record made by Lidgate and Fu, inventors of the '493 patent. Lidgate and Fu are both named authors of a Pharmaceutical Report published in September of 1987, that clearly states that octoxynol 40 was a well known ingredient in pharmaceutical products. Although Syntex contends that because this report was published five days after the priority date of the '493 patent it discloses no "prior uses" of octoxynol 40, we think it incredulous that octoxynol 40 could progress from no use, to "well known ... in pharmaceutical products" in a matter of five days. Accordingly, this report reflects that the use of octoxynol 40 in pharmaceutical compositions was known in the art at the relevant time, an important fact to consider in assessing the obviousness of the claims in suit.

2. Teaching Away

The district court clearly erred in concluding that the Waterbury, Han, and Gilbert references teach away from the use of octoxynol 40 as a nonionic surfactant in ophthalmic formulations involving NSAIDs and BAC. In addition, the district court incorrectly dismissed the relevance of the McCutcheon reference to the overall obviousness analysis. What a reference teaches or suggests must be examined in the context of the knowledge, skill, and reasoning ability of a skilled artisan. What a reference teaches a person of ordinary skill is not, as Syntex's expert appears to believe, limited to what a reference specifically

"talks about" or what is specifically "mentioned" or "written" in the reference. Under the proper legal standard, a reference will teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention. In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994). A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination, in re Fulton, 391 F.3d at 1199-1200.

The trial court found that the Waterbury reference teaches away from the use of octoxynol 40 because the only formulation disclosed in the patent did not include a surfactant, and the only surfactant mentioned in the reference was polysorbate 80. This is error because a prior art reference that does not specifically refer to one element of a combination does not, per se, teach away. If it did, only references that anticipate could be used to support an obviousness analysis. However, prior art references that are capable of rendering an invention obvious under a section 103 analysis are not limited to reference that also anticipate the patent at issue. The trial court's finding that Waterbury teaches away is also error because at col. 13, II. 44-48, Waterbury discloses "ophthalmic formulations" with "active ingredient... stabilizer, and preservative."

The Han reference was deemed to teach away because, although it disclosed the use of NSAIDs, BAC, and nonionic surfactants in ophthalmic formulations, col. 3, Example 1, the nonionic surfactants it mentioned did not include

octoxynol 40. This was error, because Han teaches NSAIDs, BAC, and nonionic surfactants. As with the Waterbury reference, the fact that octoxynol 40 was not one of the surfactants mentioned does not, without more, support the contention that the use of octoxynol 40 is nonobvious.

Gilbert, according to the district court, teaches away because it "states explicitly that a stabilizer is not preferred." Syntex. slip op. at 35. This is error because although the preferred embodiment of Gilbert does not use a stabilizer, Gilbert discloses at col. 3, II. 11-22 ophthalmic formulations that "optionally ... contain a stabilizer." Gilbert also discloses the combination of an NSAID, BAC, and a surfactant, and discloses a number of stabilizers, of which at least some, according to Apotex's expert Dr. Mitra, are nonionic surfactants.

Finally, the district court discounted the significance of the McCutcheon's reference to the use of octoxynoi 40 because although it identified octoxynoi 40 as an emulsifier and a stabilizer, it did not describe the use of octoxynoi 40 in Pharmaceuticals and indicated that it had other uses. McCutcheon's cannot be so lightly overlooked, because, as noted above, the record shows that octoxynoi 40 was previously used in Pharmaceuticals.

On remand, the district court should reevaluate the importance of these references with the understanding that they provide material disclosure and do not teach away.

3. Apotex's Expert Testimony

The district court, in concluding that the cited references teach away from combination, further found that the evidence produced no motivation to combine. While the question of whether to combine McCutcheon's with other references is a live issue on remand, there is another focus that needs to be appreciated to fully explore the obviousness issue.

As the district court appreciated, the bare question of whether it would have been obvious to substitute one surfactant for another misplaces the proper focus on the obviousness of the invention as a whole, and likely invites hindsight conclusion, forbidden by our precedent. See Gillette Co. v. S.C. Johnson & Son., Inc., 919 F.2d 720, 724-25 (Fed. Cir. 1990).

Apotex's expert testimony, however, cannot be lightly disregarded on the theory that Dr. Mitra only sought to show the obviousness of substituting octoxynol 40 for another surfactant. Mitra's testimony may be relevant on another level, which is the very point on which the examiner concluded that the otherwise suspect invention was non-obvious. Mitra's testimony has to be considered as well on the point of whether the results produced by use of octoxynol 40 are sufficiently unexpected as to secure the validity of the claims in suit.

In this case, Apotex's expert provided his theory of why a person of skill in the art would not have found it unusual to seek, find, and employ octoxynol 40 in making formulations such as those claimed in the '493 patent. Dr. Mitra explained that the references at issue informed a scientist to use water-soluble, micelle-forming,[9] nonionic surfactants act as stabilizers in a KT/BAC ophthalmic formulation.[10] He also set forth a

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[9] A micelle-forming compound has a hydrophilic side (water-loving) and a hydrophobic side (water-hating). When bound together in such a manner that they form a surface, the two sided nature of such compounds enable them to form little bubbles, known as micelles. When the micelle is formed such that the hydrophilic side is on the outside of the bubble and the hydrophobic side is on the inside of the bubble, a sufficiently large micelle can encapsulate hydrophobic compounds inside the bubble. A micelle formed in this manner can enable otherwise insoluble compounds to dissolve in water.

[10] In his Expert Report, Dr. Mitra stated that "[t]he Waterbury "151 patent shows that the non-ionic surfactant polysorbate 80 soiubilizes BAC. Therefore, one would expect that other non-ionic surfactants such as octoxynol 40, function as a surfactant." Dr. Mitra also stated that

> [b]y the time of the claimed invention on or before 1987, one of ordinary skill in the art of ophthalmic pharmaceutical formulations would have known that.... non-ionic surfactants, such as polysorbate 80, were used in ophthalmic formulations as a surface active agent as a solubilizer, to increase spreading and to reduce surface tension. Octoxynol 40 was known as a non-ionic surfactant as shown by Grant & Hackh's

scientific rationale for the informed selection of certain nonionic surfactants, and testified that octoxynol 40 was known and used in many

products, including cosmetics.[11] Dr. Mitra also opined that knowledge of the chemical qualities of surfactants useful to the claimed subject matter would cause a person, "as a matter of science" to "go into another nonionic surfactant like octoxynols."

To be clear, we do not require that the district court credit all (or any) of this testimony. On remand, however, the district court should consider Apotex's claim of obviousness in light of the applicable legal principles and unencumbered by the factual errors identified above.

4. The Prosecution History

The prosecution history makes clear that the PTO initially believed a person of ordinary skill in

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Chemical Dictionary - Fifth Edition, McGraw-Hill, 1987 and GAF product brochures.

[11] Dr. Mitra concluded that "[t]he Waterbury '151 patent shows that the nonionic surfactant polysorbate 80 solubilizes BAC. Therefore, one would expect that other non-ionic surfactants would work equally well and one would thus look to other patents/publications which show that other non-ionic surfactants such as octoxynol 40, function as a surfactant." Dr. Mitra so concluded because the stabilizer disclosed in Waterbury, polysorbate 80, was a water-soluble, micelle-forming, nonionic surfactant. Dr. Mitra opined that since octoxynol 40 is also a water-soluble, micelle-forming, nonionic surfactant, both compounds are capable of solubilizing the KT/BAC complex by encapsulation.

the art would know to use a nonionic surfactant that possessed the qualities of octoxynol 40 in the claimed formulation. In an Office Action dated April 28, 1989, the examiner rejected claims in the '173 parent application directed to the formulation containing octoxynol 40 because "it is known to use nonionic surfactants." In particular, the examiner stated: 'The mere substitution of one nonionic [surfactant] for another, that is, [octoxynol 40] for the nonionic of the primary reference is not deemed a patentable distinction in the absence of some unobvious result."

Syntex responded to this rejection by providing data from a test comparing the efficacy of octoxynol 40, polysorbate 80, and myrj 52, purportedly demonstrating unexpected results. The PTO examiner deemed this showing insufficient:

> It has not been shown that the claimed nonionics provide any unexpected results over the nonionics of the primary references. The data at page 5 of the response shows only that "octoxynol 40" gave somewhat better results than some conventional nonionic surfactants. However, these data do not compare "octoxynol 40" to the nonionics of the primary references. Furthermore the concentrations of the Octoxynol 40 is [sic] greater than that of the other nonionic surfactants. Therefore, no conclusion can be drawn from said data. Also the showing is not commensurate with the claims which, except for claims 8, 9, and

> 13, recite no proportions and broadly set forth the NSAID, quarternary ammonium preservative and polyoxyethylatedoctylphenol surfactant. Finally, the data (1) do not specify the amount of the NSAID and (2) are not in declaration form. The response therefore does not overcome the rejection.

(Emphases added). The '173 parent application was ultimately abandoned.

The '027 continuation application was assigned to a different PTO examiner. In an Office Action dated February 25, 1991, the new examiner entered the same rejection, restating, verbatim, that: "The mere substitution of one nonionic [surfactant] for another, that is, [octoxynol 40] for the nonionic of the primary reference is not deemed a patentable distinction in the absence of some unobvious result."

Syntex responded by stating that it had "shown in the prosecution of the parent to this application [the '173 parent application] that other nonionic surfactants, such as [polysorbate 80] and myrj, fail to act as stabilizers in the claimed formulations." This statement contradicted the express finding of the initial PTO examiner that Syntex's earlier data failed to show unexpected results. Whether the second examiner was aware of the earlier rejection of Syntex's claims is unknown. But the relevance of the inconsistency

between the views of two examiners is not insignificant.

Syntex supported its view of unexpected results with the Lidgate Declaration, which contained test data purporting to demonstrate the unexpected superiority of octoxynol 40 in comparison to other octoxynols. The applicant's declaration averred that octoxynol 40 is satisfactory for use in the claimed formulation while octoxynols 3 and 5 are unsatisfactory. The Lidgate Declaration, however, omitted data showing that octoxynol 40 did not "outperform other surfactants." The record shows that Syntex knew that, when compared, octoxynol 12.5 and octoxynol 40 produced test samples that "looked equivalent at all temperatures." In addition, the '493 patent itself discussed the use of a shorter chain octoxynol, octoxynol 10, in the disclosed formulations. Although we conclude, later in this opinion, that Syntex did not commit inequitable conduct as charged (notably, Apotex never asserted that Syntex's arguments to the second examiner are suspect), we think the unvarnished view of the prosecution history shows some weakness in the conclusion that the patentee established unexpected results for the claimed surfactant.

While we recognize that an issued patent is entitled to the presumption of validity, 35 U.S.C. § 282, and that a challenger's burden to show invalidity is more difficult to satisfy when prior art references have been presented to the PTO, Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 447 (Fed. Cir. 1986), we think this case is

unusual because certain key facts existed that give rise to some doubt as to the strength of the factual proposition that octoxynol 40 indeed produced unexpected results. With full respect for the general propositions that the issued patent is entitled to a presumption of validity, and that the examiners are expected to perform reasonably, see Bausch & Lomb, 796 F.2d at 447 (we assume that the patent examiner has some expertise in interpreting the references and some familiarity with the level of skill in the art), on remand the district court should review the file history as part of its assessment of whether the invention claimed by the claims in suit are nonobvious.

5. Commercial Success

Given the error in its fact finding, the district court should also reevaluate its analysis of the secondary considerations. The district court appeared to rely heavily on the commercial success of ACULAR. As discussed in Merck, the secondary consideration of commercial success exists largely to provide a means for patentees to show in close cases that subject matter that appears obvious is in law unobvious because a high degree of commercial success permits the inference that others have tried and failed to reach a solution. Merck, 395 F.3d at 1376. In Merck, we held that evidence of commercial success resulted in a particularly weak inference because prior art patents prevented others from competing to reach the solution embodied in the claims at issue. 395 F.3d at 1376-77.

Based on the record, we are of the view that the district court should consider the impact of the Merck analysis on this case. Assuming that the active ingredient in the formulation was previously patented, the commercial success of ACULAR may heavily derive from subject matter that does not on the whole contribute to the patentable distinctiveness of these claims. In such a case, the trial court should carefully consider whether the nexus requirement of our law is satisfied. See In re Huang, 100 F.3d 135 (Fed. Cir. 1996).

D. Inequitable Conduct

This court has held that a breach of the duties of candor, good faith, and honesty when prosecuting patent applications constitutes inequitable conduct. Molins PLC, 48 F.3d at 1178. "[Unequitable conduct during the prosecution of a patent application renders the subsequently issued patent unenforceable." Life Techs.. Inc. v. Clontech Lab., Inc.. 224 F.3d 1320, 1324 (Fed. Cir. 2000). Affirmative misrepresentations of a material fact coupled with an intent to deceive can constitute inequitable conduct. See Molins, 48 F.3d at 1178. "Materiality and intent to deceive are distinct factual inquiries, and each must be shown by clear and convincing evidence." Life Techs., 224 F.3d at 1324. Prior to March 16, 1992, this court "held that materiality for purposes of an inequitable conduct determination required a showing that a reasonable examiner would have considered such [data] important in deciding whether to allow the

patent application.'"[12] Davco Prods., Inc. v. Total Containment. Inc., 329 F.3d 1358,1363 (Fed. Cir. 2003). In making the ultimate determination of inequitable conduct, the trial court "must conduct a balancing test between the levels of materiality and intent, with a greater showing of one factor allowing a lesser showing of the other." id.

Apotex argues that Syntex's submission of the Lidgate Declaration and the test results excluding data on octoxynol 12.5 constituted inequitable conduct. The district court rejected this argument finding the omitted test results lacking in materiality and finding no intent to deceive the PTO. The district court concluded that test results concerning octoxynol 12.5 were not material because (1) the purpose of the declaration was to show that not all octoxynols would work, not that octoxynol 40 was the only octoxynol that would stabilize the formulation; (2) octoxynol 5 was the closest prior art mentioned by the examiner; and (3) the '493 patent disclosed the potential use of octoxynol 10 as a surfactant thereby putting the examiner on notice that octoxynol 40 was not the only possible useful surfactant.

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[12] The '027 application was filed on December 7, 1990, and the '493 patent issued on May 5, 1992. In 1992, the rule regarding the standard for materiality of disclosures made to the PTO during prosecution changed. Because the PTO issued its notice of allowability regarding the Lidgate Declaration on December 3, 1991, the previous standard was in effect at all relevant points. Consequently, it is not necessary for us to address the import of this change in standard.

The district court also concluded that Lidgate, Freyberg, and Fu, the inventors of the '493 patent, lacked intent to deceive the PTO. The district court found the testimony of these individuals to be credible. It also found that Apotex failed to establish by clear and convincing evidence that these individuals breached their duty of good faith and candor to the PTO.

Credibility determinations are the type of factual determinations that are best left to the fact finder, the trial court. Apotex points to no evidence that the district court failed to consider Syntex's conduct, but rather asks us to replace the court's credibility determinations with our own. We decline to do so and find no clear error in the district court's finding of no intent to deceive.

The withheld test results showing that octoxynol 12.5 was capable of stabilizing the KT/BAC formulation, while material to Lidgate's statement that octoxynol 40 was generally superior to other octoxynols in stabilizing the KT/BAC formulation, was not sufficiently material to overcome the insufficient showing of intent.

Given that both materiality and intent must be found and that there was no clear error in the district court's finding of intent, the determination of no inequitable conduct is affirmed.

E. Infringement Analysis

Since we reverse the district court's finding that the '493 patent is nonobvious,

we do not reach the question of whether Apotex's submission of an ANDA for a generic version of ACULAR constitutes an act of patent infringement under 35 U.S.C. §271(e).

CONCLUSION

We affirm the district court's determination that there was no inequitable conduct in the prosecution of the '493 patent. We also affirm the district court's claim interpretation. However, because the district court committed clear error in the findings underlying its determination of nonobviousness, we reverse the court's nonobviousness determination and remand that issue to the district court for further consideration of obviousness. Accordingly, the judgment of the district court is

AFFIRMED-IN-PART, REVERSED-IN-PART AND REMANDED-IN-PART.

COSTS

Each party shall bear its own costs.

United States Court of Appeals for the Federal Circuit

04-1252

SYNTEX (U.S.A.) LLC and ALLERGAN, INC.,

Plaintiffs-Appellees,

v.

APOTEX, INC., APOTEX CORP., and NOVEX PHARMA,

Defendants-Appellants.

PROST, Circuit Judge, concurring.

I agree with the majority's well-reasoned analyses with respect to almost all of issues raised in this case, as well as the majority's decision to remand this case to the district court for reconsideration of whether the '493 patent is invalid for obviousness. I write separately only to point out my disagreement with one particular portion of the majority's opinion.

I respectfully disagree with the opinion's focus on the proceedings at the Patent and Trademark Office ("PTO") when analyzing whether the district court correctly found that the claimed ophthalmic formulation produced unexpected results. The majority analyzes the prosecution history of the '493 patent, pointing out an "inconsistency between the views of two examiners"

in the parent and continuation applications and a statement during prosecution that the majority believes "contradicted the express finding of the initial PTO examiner." Ante, at 20. In light of these aspects of the prosecution history, the majority concludes that "this case is unusual because key facts existed that give rise to some doubt as to the strength of the factual proposition that octoxynol 40 indeed produced unexpected results" and instructs the district court to "review the file history as part of its assessment of whether the invention claimed by the claims in suit are nonobvious." Ante, at 21. Thus, the majority requires that the district court analyze the views of separate examiners at the PTO and review statements made by the patent prosecutor for possible mischaracterizations of the prosecution history.

I view this investigation into the prosecution history as problematic in several respects. First, this investigation shifts the focus from the appropriate question for the district court to address on remand: whether the evidence shows the '493 patent claims an ophthalmic formulation that produced unexpected results. Next, as the majority concedes, ante, at 20, Apotex never asserted that Syntex's arguments to the second examiner concerning the prosecution history are suspect. Moreover, had Apotex asserted that these arguments were suspect, I believe the assertion would be relevant to the issue of inequitable conduct and not obviousness. In this regard, I don't view the statement referred to by the majority as a clear mischaracterization of the prosecution history. And the patent prosecutor

likely believed the previous data submitted to the first examiner did show unexpected results even if the first examiner believed the data did not. I also find it hard to believe that the second examiner was somehow duped into thinking that the first examiner agreed that the previous data showed unexpected results even if the statement could be understood to be misleading.

In general, I fail to see how the conduct of a patent applicant is relevant to an obviousness determination. Alleged misconduct at the PTO, in terms of either mischaracterizations or omissions, goes to the heart of an inequitable conduct inquiry but is simply irrelevant to an obviousness inquiry. That is not to say that if evidence showing that a claimed invention does not produce unexpected results was not disclosed to the PTO then that evidence should not be considered by the district court in its obviousness analysis. On the contrary, a district court should consider evidence relevant to an obviousness analysis even if that evidence is not disclosed to the PTO.

In sum, I believe that, here, the district court should address the evidence in the record to determine whether the claimed ophthalmic formulation showed unexpected results. For example, the district court should review all of Lidgate's test results, including test results not disclosed to the PTO such as the comparison of octoxynol 12.5 with octoxynol 40, as well as Dr. Mitra's reasons to discredit some of those test results. In my view, however, there is nothing so unusual about this case as to compel the district

court on remand to review alleged misconduct by the patent applicant at the PTO.

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

04-1252

SYNTEX (U.S.A.) LLC and ALLERGAN, INC.,

Plaintiffs Appellees,

v.

APOTEX, INC., APOTEX CORP, and NOVEX PHARMA,

Defendants-Appellants.

ORDER

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

[Entered June 13, 2005]

ORDER

Before CLEVENGER, Circuit Judge, GAJARSA, Circuit Judge, and PROST, Circuit Judge.

A petition for rehearing having been filed by the APPELLANTS,

UPON CONSIDERATION THEREOF, it is

ORDERED that the petition for rehearing be, and the same hereby is, DENIED.

The mandate of the court will issue on June 20, 2005.

FOR THE COURT,

Jan Horbaly
Clerk

Dated: June 13, 2005

cc: Robert S. Silver
Alexander L. Brainerd

SYNTEX USA V APOTEX, 04-1252
(DCT – 01 – CV - 2214)

Note: Pursuant to Fed. Cir. R. 47.6, this order is not citable as precedent. It is a public record.

FILED
DEC 29 2003
RICHARD W. WIEKING
CLERK, U.S. DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

SYNTEX (U.S.A.) LLC, a Delaware corporation and ALLERGAN, INC., a Delaware corporation,

Plaintiffs,

v.

APOTEX, INC., a Canadian corporation, APOTEX CORP., a Delaware corporation, and NOVEX PHARMA, a Canadian corporation,

Defendants.

Case No. 01-2214 MJJ
FINDINGS OF FACT AND CONCLUSION OF LAW

INTRODUCTION

Plaintiffs Syntex (U.S.A.) LLC ("Syntex") and Allergan, Inc. ("Allergan") have sued Defendants Apotex, Inc., Apotex Corp., and Novex Phanna ("Defendants") for infringement of U.S. Patent No. 5,110,493 (the "'493 patent") entitled "Ophthalmic NSAID Formulations Containing a Quaternary

Ammonium Preservative and a Nonionic Surfactant" The '493 patent claims ophthalmic formulations useful for treating eye inflammation, methods of using such formulations to treat ophthalmic disease, and preservative systems for use in such formulations. The '493 patent issued from Application No. 07/624,027, which was filed on December 7,1990 and which was a continuation of Application No. 07/096,173, filed on September 11,1987. The joint inventors of the '493 patent were Dr. Roger Fu and Deborah Lidgate. Syntex is the owner of the '493 patent. Allergan is Syntex's exclusive distributor and has exclusive rights to manufacture the ketorolac tromethamine ophthalmic formulations claimed in the '493 patent. Allergan has been making and selling an ophthalmic solution under the trade name ACULAR® since the New Drug Application ("NDA") for a 0.5% ketorolac tromethamine ophthalmic formulation was approved by the Food and Drug Administration ("FDA") in 1992.

Defendants are manufacturers of generic pharmaceuticals. On April 25, 2001, Novex Pharma notified Syntex and Allergan that it had filed Abbreviated New Drug Application ("ANDA") 76-109 with the FDA, seeking approval to market a generic version of ACULAR® in the United States. Trial Ex. E. In its notice, Novex Phanna alleged that the '493 patent is invalid, unenforceable, and not infringed by Novex Pharma's proposed drug. Syntex and Allergan then sued Defendants under 35 U.S.C. § 271(e)(2), which provides that the filing of an ANDA for approval to make, market, or sell a drug claimed in a patent, or the use of which is claimed in a patent, is an act of patent infringement

Defendants contend that they do not infringe the '493 patent and that the '493 patent is invalid for lack of utility, lack of enablement, indefiniteness, and obviousness. Defendants also contend that the '493 patent is unenforceable because Syntex committed inequitable conduct in the prosecution of the '493 patent

Both parties seek attorneys fees and costs.

Defendants also sought an Order declaring that (1) Defendants' ANDA does not infringe any of the claims of the 493 patent and (2) the effective date of the approval of Defendants' ANDA is immediate under Section 505(j) of the Federal, Food, Drug and Cosmetic Act, 21 U.S.C. Section 355(j), for its 0.5 ketoralic tromethamine ophthalmic formulation and its use.

In its order of March 19, 2003, this Court found that the submission of ANDA 76409 infringed each claim of the '493 patent and granted Plaintiffs' motion for partial summary judgment that Defendants had literally infringed each claim of the '493 patent

This case was tried to the Court without a jury. Plaintiffs were represented by Alexander L. Brainerd, Keith R. Weed, and Christine Saunders Haskett of Heller Ehrman White & McAuliffe LLP, and Defendants were represented by Alan H. Bernstein, Robert S. Silver, and William J. Castillo of Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd. and Ronald S. Lemieux of Squire, Sanders & Dempsey L.L.P. The evidentiary portion of the trial commenced on June 2, 2003 and concluded on June 20, 2003.

Thereafter, the parties argued the matter and submitted the same to the Court along with their proposed Findings of Fact and Conclusions of Law. After a review of the evidentiary record, the exhibits admitted by the Court, and having fully considered the arguments of counsel, the Court now enters the following Findings of Fact and renders its Conclusions of Law.[1]

II. INFRINGEMENT OF THE '493 PATENT
FINDINGS OF FACT

1. On May 5, 1992, the 493 patent entitled "Ophthalmic NSAID Formulations Containing a Quaternary Ammonium Preservative and a Non-ionic Surfactant," issued to Syntex (U.S.A.) Inc., having been assigned by inventors Dr. Roger Fu and Ms. Deborah Lidgate. Trial Exh. 01.

2. There are three types of claims in the '493 patent: claims to formulations (Claims 1-7), claims to methods of treating disease by using the formulations of Claims 1-7 (Claims 8-14) and claims to a preservative system (Claims 15 and 16). Claims 1, 8 and 15 are the only independent claims in the '493 patent.

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[1] The Court has read and considered Plaintiffs' motion under Rule 52 and denies the same. The Court finds that on this record, Defendants have marhsalled sufficient evidence to defeat Plaintiffs' motion in all respects. In reaching this conclusion, the Court has considered Defendants' Sur-Reply and accordingly grants Defendants' request to consider the same.

3. Independent Claim 1 claims "[a]n ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation, comprising:

> an ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug in an effective amount for ophthalmic treatment between 0.001% and 10.0% wt/vol;[2]
>
> a quaternary ammonium preservative in an antimicrobially effective amount between 0.001% and 1.0% wt/vol;[2]
>
> an ethoxylated alkyl phenol that conforms generally to the formula:

$C_8H_{17}C_6H_4(OCH_2CH_2)NOH$ where n has an average value of 40 in a stabilizing amount between 0.001% and 1.0% wt/vol; and an aqueous vehicle q.s. [quantity sufficient] to 100%.[3]

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[2] Under the parties' agreed definition, "ophthalmologically acceptable" means "non-irritating to the eye and having an active ingredient that penetrates the blood-aqueous barrier and/or diffuses through the various ocular substructures to the site where it is pharmacologically active."

[3] "Octoxynol 40" is a shorter term for the claim element "an ethoxylated alkyl phenol that conforms generally to the formula: $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$ where n has an average value of 40."

Thus, Claim 1 claims a combination of at least four ingredients: a type of drug, a type of preservative, Octoxynol 40, and water.[4]

4. Dependent Claim 2 claims the formulation of Claim 1 wherein the quaternary ammonium preservative is benzalkonium chloride ("BAC"); dependent Claim 3 claims the formulation of Claim 2 wherein the ophthalmologically acceptable non-steroidal anti- inflammatory carboxyl group-containing drug[5] is selected from the group selected from ketorolac, indomethacin, flurbiprofen, and suprofen; dependent Claim 4 claims the formulation of Claim 3 wherein the ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is ketoroiac tromethamine; and dependent Claim 5 claims the formulation of Claim 1, further comprising a chelating agent in an amount between 0.01% and 1.0% wt/vol; a tonicifier q.s. to achieve isotonicity with lacrimal fluid; and 1N NaOH or 1N HC1 q.s. to adjust pH to7.4"0.4.

5. Dependent Claims 6 and 7 claim specific compositions included within Claim 1, wherein the ophthalmologically acceptable non-steroidal anti-

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[4] The combination is of "at least four ingredients" because the use of the word "comprising" at the end of the preamble makes this an "open" claim, which is infringed by any combination that includes the claimed elements, even if other ingredients are also present. *See Vivid Technologies, Inc.* v. *American Science & Engineering, Inc.*, 200 F.3d 795, 811 (Fed Cir. 1999).

[5] "Non-steroidal anti-inflammatory drug" is sometimes abbreviated as "NSAID."

inflammatory carboxyl group- containing drug (Claim 6) or ketoroiac tromethamine (Claim 7) is present at 0.50% wt/vol; BAC is present at 0.02% wt/vol (of a 50% aqueous solution); Octoxynol 40 is present at 0.01% wt/vol (of a 70% aqueous solution); Na^2EDTA is present at 0.10%; NaC1 is present either at q.s. for isotonicity with lacrimal fluid (Claim 6) or at 0.79% wt/vol (Claim 7); the pH is adjusted to 7.4"0.4; and purified water is present at q.s. to 100%. Thus, Claims 6 and 7 are more specific than Claims 1-5, requiring formulations of specific ingredients in specific amounts.

6. The method of treatment claims of the '493 patent begin with independent Claim 8. Claim 8 claims "[a] method of treating an ophthalmic disease caused by, associated with, or accompanied by inflammatory processes, comprising administering to a mammal suffering therefrom a formulation comprising" the formulation of Claim 1. Dependent method Claims 9-14 claim the method of Claim 8 using the formulations of Claims 2-7, respectively. Thus, Claims 13 and 14 claim methods of treating ophthalmic disease by administering the very specifically claimed formulations of Claims 6 and 7.

7. Claims 15 and 16 are the preservative system claims. Independent Claim 15 claims "[a]n antimicrobially effective preservative system for an ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drag formulation, comprising: a quaternary ammonium preservative in an antimicrobially effective amount between 0.001% and 1.0% wt/vol of the formulation; and [Octoxynol 40] in a stabilizing amount between

0.001% and 1.0% wt/vol of the formulation." Dependent Claim 16 claims the preservative system of Claim 15 wherein the preservative is BAC.

8. Syntex submitted an NDA to the FDA, pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act, seeking approval to market and sell a 0.5% ketorolac tromethamine ophthalmic solution" the drug that became ACULAR®. In 1992, the FDA approved ACULAR® for the treatment of ocular itch associated with seasonal allergic conjunctivitis. In 1997, the FDA approved ACULAR® for use in the treatment of postoperative inflammation. R.T. 1272:9-1274:15.

9. ACULAR® is a sterile isotonic aqueous solution with a pH of 7.4. ACULAR® contains 0.5% wt/vol ketorolac tromethamine; 0.01% wt/vol BAC; 0.007% wt/vol Octoxynol 40; 0.1% wt/vol edetate disodium, a chelating agent; 0.79% wt/vol sodium chloride; hydrochloric acid and/or sodium hydroxide to adjust the pH; and purified water. ACULAR® includes each element of each of Claims 1-7 and 15-16 of the '493 patent, and the uses of ACULAR® include each element of each of Claims 8-14 of the '493 patent. Claim 7 of the '493 patent claims the ingredients of ACULAR® exactly, and Claim 14 of fhe '493 patent claims the use of ACULAR® exactly. Trial Ex. 085; RX 1534:10-1536:14.

10. Defendants' ANDA 76-109 specifies that Defendants seek to market a drug that is identical to ACULAR® in its composition, preservative system, and intended uses. Trial Ex. 058. The ANDA 76-109 formulation contains 0.5% wt/vol ketorolac

tromethamine; 0.02% wt/vol BAC in the form of a 50% aqueous solution; 0.01% wt/vol Igepal CA-897, a 70% aqueous solution of Octoxynol 40; 0.1% wt/vol edetate disodium; 0.8% wt/vol sodium chloride, a tonicifier; an amount of IN sodium hydroxide or hydrochloric acid sufficient to adjust the pH to 7.3-7.5; and purified water in a quantity sufficient to bring the formulation to its desired volume. ANDA 76-109 at N0125, N0128-N0129, N0156-N0159. ANDA 76-109 seeks approval to use this formulation to treat human beings for "temporary relief of ocular itching due to seasonal allergic conjunctivitis" and for 'treatment of postoperative inflammation." ANDA 76-109 at N0011. The formulation is to be applied directly to me eye. ANDA 76-109 at N0101.

11. The Court has found that the formulation defined by ANDA 76-109 satisfies every limitation of Claims 1-6, 8-13, and 15-16 of the '493 patent. Order Granting Plaintiffs' Motion for Partial Summary Judgment on Infringement, Denying Defendants' Motion for Summary Judgment of Invalidity, filed March 19,2003, at 4-5; Plaintiffs' Memorandum of Points and Authorities in Support of Motion for Partial Summary Judgment of Infringement of U.S. Patent No. 5,110,493, Appendix A.

CONCLUSIONS OF LAW

12. Submission of an ANDA is an act of patent infringement if the ANDA seeks approval to manufacture, use, or sell a drug that is claimed in a patent or the use of which is claimed in a patent. 35 U.S.C. § 271(e) provides:

> (2) It shall be an act of infringement to submit -
> (A) an application under section 505(J) of the Federal Food, Drug, and Cosmetic Act[6] or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent,... if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug or veterinary biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent

13. In deciding a claim of infringement under Section 271(e)(2), a court must employ a traditional infringement analysis. *See Glaxo, Inc.* v. *Novopharm, Ltd.*, 110 F.3d 1562, 1567 (Fed. Cir. 1997) ("The plain language of the statute does not alter a patentee's burden of proving infringement").

14. Such a traditional infringement analysis involves two steps. *See Karlin Technology, Inc.* v. *Surgical Dynamics, Inc.*, 177 F.3d 968, 971 (Fed. Cir. 1999). The first step is to construe, or interpret, the claims of the patent; this claim construction step presents a matter of law for the Court to decide. *See Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 372 (1996). The second step is to compare the accused device or process" in this case, the drag formulations and uses of the formulations described in

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[6] An ANDA is an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act. *See* 21 U.S.C. §355 (j).

ANDA 76-109" to the properly construed claims. The accused device literally infringes the claims if every limitation of the properly construed claims is found in the accused device. *See Karlin,* 177 F.3d at 974. Alternatively, the accused product infringes the claims under the doctrine of equivalents if the differences between the two are deemed "insubstantial" by one of ordinary skill in the art. *See Catalina Marketing International, Inc. v. Coolsavings.com, Inc.,* 289 F.3d 801, 812-13 (Fed. Cir. 2002) (explaining that one test of "insubstantial" differences is whether the accused product "performs substantially the same function in substantially the same way to obtain the same result as the claim limitation*').

15. In this case, the parties contested the meaning of two terms of the '493 patent: "stabilizing amount" (in the phrase "[Octoxynol 40] in a stabilizing amount between 0.001% and 1.0% wt/vol") and "antimicrobially effective" (in the phrase "quaternary ammonium preservative in an antimicrobially effective amount between 0.001% and 1.0% wt/vol"). Defendants' position was that these two phrases are claim limitations. Plaintiffs' position was that the two contested terms were not claim limitations. The parties did not contest the meaning of any other claim terms. Joint Claim Construction Statement and Prehearing Statement, filed January 9,2002.

16. The Court held a *Markman* claim construction hearing on September 13,2002 and issued its Claim Construction Order on November 19,2002. *See Markman,* 517 U.S. at 372. In that Order, the Court ruled that the two contested phrases were not

claim limitations but merely expressed the intended results of using the claimed ingredients in the claimed amounts.

17. "Stabilizing amount" (as used in the phrase "[Octoxynol 40] in a stabilizing amount between 0.001% and 1.0% wt/vol") and "antimicrobially effective" (as used in the phrase "quaternary ammonium preservative in an antimicrobially effective amount between 0.001% and 1.0% wt/vol") are not limitations of the claims of the '493 patent

18. In deciding Plaintiffs' Motion for Partial Summary Judgment regarding infringement ofthe '493 patent, the Court compared the claims of the '493 patent with the drug formulation and uses set forth in Defendants' AND A 76-109. The Court determined that there was no genuine issue of material fact as to whether the submission of AND A 76-109 meets the limitations of the claims of the '493 patent and on that basis granted Plaintiffs' motion.

19. In ANDA 76-109, Defendants seek approval for the commercial manufacture, use, and sale of a drug claimed in each of Claims 1-7 of the '493 patent.

20. In ANDA 76-109, Defendants seek approval to use the drug formulation claimed in each of Claims 1-7 of the '493 patent to treat human beings for "temporary relief of ocular itching due to seasonal allergic conjunctivitis" and for "treatment of postoperative inflammation." ANDA 76-109 at N0011. Accordingly, Defendants' ANDA seeks approval for

the use of a method claimed in each of Claims 8-14 of the '493 patent.

21. In ANDA 76-109, Defendants seek approval for the commercial manufacture, use, and sale of a drug that contains a preservative system claimed in Claims 15-16 of the '493 patent

22. Although there is a slight difference between the ANDA formulation and the composition set forth in Claims 7 and 14 of the '493 patent (in that Claims 7 and 14 specify a sodium chloride concentration of 0.79% and the ANDA formulation contains 0.8% sodium chloride), Claims 7 and 14 are infringed under the doctrine of equivalents. A concentration of 0.79% sodium chloride is not substantially different from a concentration of 0.8% sodium chloride.

23. Defendants' ANDA also induces infringement of the method of use claims of the '493 patent (Claims 8-14). A defendant is liable for inducement of infringement when it "knowingly aided and abetted another's direct infringement of the patent" *Warner-Lambert Co.* v. *Apotex Corp.*, 316 F.3d 1348, 1363 (Fed. Or. 2003). 35 U.S.C. §271(e)(2) supports an action for induced infringement as well as an action for direct infringement. *See Allergan, Inc.* v. *Alcon Laboratories, Inc.*, 324 F.3d 1322, 1331 (Fed. Cir. 2003).

24. Defendants' ANDA 76-109, which describes a formulation meeting all of the limitations of Claims 1-7 of the '493 patent, also describes uses of that formulation claimed in Claims 8-14 of the '493

patent. ANDA 76-109 at N0011. Accordingly, ANDA 76-109, standing alone, demonstrates Defendants' inducement of infringement of the '493 patent's method claims. *See Warner-Lambert,* 316 F.3d at 1364 ("The infringement case is ... limited to an analysis of whether what the generic drug maker is requesting authorization for in the ANDA would be an act of infringement if performed."). Moreover, Defendants will intentionally encourage doctors to infringe Claims 8-14 of the '493 patent once ANDA 76-109 is approved. Thus, Defendants have induced infringement of Claims 8-14 of the '493 patent under 35 U.S.C. § 271(e)(2).

25. Defendants' ANDA 76-109 is for a drug claimed in each of Claims 1-7 and 15-16 of the '493 patent and the use of which is claimed in each of Claims 8-14 of the '493 patent. Therefore, Defendants, and each of them, have directly infringed Claims 1-7, 8-14, and 15-16 of the '493 patent and have also induced the infringement of Claims 8-14 of the '493 patent. *See* 28 U.S.C. §271(e)(2)(A).

III. UTILITY
FINDINGS OF FACT

26. The '493 patent sets forth, in a section entitled "Utility and Administration" the utility of the claimed inventions as follows:

> This invention is directed to NSAID ophthalmic formulations and a method useful for treating ophthalmic diseases in mammals. These diseases are either caused by, associated with or

> accompanied by inflammatory processes including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury. The method of this invention is both curative and preventative. When applied, for example, pre-surgically or immediately post-traumatically, i.e. before inflammation develops, it prevents development of inflammation. When applied directly to the eye suffering from any of the named ophthalmic diseases, it suppresses already developed inflammatory processes.

'493 patent, column 5, lines 51-65.

27. Syntex submitted an NDA to the FDA, seeking approval to market and sell a 0.5% ketoroiac tromethamine ophthalmic solution, ACULAR®, mat embodies the claims of the '493 patent. In 1992, the FDA approved ACULAR® for the treatment of ocular itch associated with seasonal allergic conjunctivitis. In 1997, the FDA approved ACULAR® for use in the treatment I of postoperative inflammation. Thus, the FDA has determined that ACULAR® is effective for these two indications. R.T. 1272:9-1274:15.

28. The studies submitted by Plaintiffs in support of the NDA showed that formulations containing ketoroiac tromethamine at concentrations

within the claims of the '493 patent were useful in treating ophthalmic diseases in mammals. Trial Exs. 070, 071, 074, 075, 078, 079, 153.

29. Plaintiffs introduced evidence, in the form of animal and clinical studies, showing that ketoroiac tromethamine concentrations of as low as 0.01% wt/vol and including 0.03%, 0.1%, 0.25% and 0.5% wt/vol had anti-inflammatory activity in mammals. The evidence also showed that concentrations of ketoroiac tromethamine as high as 4% were well tolerated in at least some mammals. Trial Exs. 074, 078, 079, 080; R.T. 1306:7-1307:12,1308:19-1321:11, 1323:15-1328:25, 1348:12-1349:5.

30. Clinical studies on ketoroiac tromethamine ophthalmic solutions conducted at 10 Allergan showed that 0.1% ketorolac ophthalmic solutions were effective in relieving post-cataract inflammation and that 0.4% ketorolac ophthalmic solutions were safe and effective in the treatment of ocular pain. Trial Exs. 070, 071, 152, 153 at AGN029769; R.T. 1265:7-1270:5, 1274:16-1277:23, 1284:18-1285:6, 1292:13-1295:7.

31. On May 30,2003, Allergan received approval from the FDA for a 0.4% wt/vol ketorolac tromethamine ophthalmic formulation, demonstrating that the FDA found such a formulation to be safe and efficacious "for the reduction of ocular pain and burning/stinging following corneal refractive surgery." Trial Ex. 304; R.T. 1264:2-1265:12. The 0.4% ketorolac tromethamine solution approved by the FDA contained 0.4% wt/vol ketorolac tromethamine, 0.006% wt/vol BAC, 0.003% wt/vol Octoxynol 40, 0.79% wt/vol

sodium chloride, and 0.015% wt/vol EDTA, and was pH-adjusted to 7.4. R.T. 1377:18-1378:17.

32. ACULAR®'s sales climbed from $18 million in 1994 to over $58 million in 2001, for a total of $291 million in net sales during that period, and ACULAR®'s market share among ophthalmic anti-inflammation drugs grew from 15.1% in 1993 to 36.1% in 2000. Upon entering the marketplace, ACULAR® very quickly achieved a greater market share than its major competitor drug, Voltaren. Trial Exs. 090, 091; R.T. 1541:13-1555:14, 1558:23-1562:18.

33. As explained in the previous section, Defendants have infringed all sixteen claims of the '493 patent. Also as noted above, Defendants' ANDA 76-109 specifies that Defendants seek to market a drug that is identical to ACULAR® in its composition, preservative system, and intended uses. Trial Ex. 058.

34. In connection with the filing of their ANDA, Defendants were required to, and did, certify to the FDA that their proposed generic version of ACULAR® was safe and efficacious in the treatment of ophthalmic disease. R.T. 84:22-86:12.

35. Prior to the invention of the '493 patent, it was generally known in the field of pharmaceutical formulation that carboxyl group-containing NSAIDs were incompatible with quaternary ammonium preservatives, such as BAC. The interaction between carboxyl group- containing NSAIDs and quaternary ammonium preservatives results in two potential problems. First, a solution containing both ingredients might become cloudy or turbid and thus unacceptable

for ophthalmic formulations. Second, the preservative might be inactivated so that it would no longer perform its function. Trial Ex. 156, 158, 224, 225, 227; R.T. 794:19-795:3, 813:17-814:5, 1374:24-1377:12, 1642:23-1645:16, 1665:3-1670:12.

36. It is important for pharmaceutical formulations, not just to be stable, but to have a "robust" stability. The stability of any pharmaceutical formulation will be affected by such changes as a change in environmental conditions (such as changes in temperature and humidity), a change in pH, a change in packaging, and a change in the quality or composition of the components of the formulation. A robust formulation is necessary, therefore, to be able to withstand these types of changes. R.T. 1634:16-1639:6.

37. The stability of a solution of ketorolac tromethamine and BAC will be heavily dependent on the type of BAC that is used. Because BAC is not a pure substance, but is made up of a mixture of homologs" that is, molecules that are similar but that have varying lengths" the source of the particular BAC that is used will have a significant effect on the concentrations of ketorolac tromethamine and BAC at which a complex is formed. R.T. 1647:24-1649:1, 1670:2-1676:4. Trial Exh. 306.

38. Tests performed by Defendants' expert, Dr. Mitra, demonstrated that ketorolac tromethamine and BAC are incompatible and that the addition of Octoxynol 40 to the solution provided for a clear solution. In particular, Dr. Mitra's tests showed that a solution containing 0.2% wt/vol ketorolac

tromethamine and 0.02% wt/vol BAC was very turbid. When 0.01% wt/vol Octoxynol 40 was added to that solution, the solution became clear. This demonstrates that Octoxynol 40 plays a stabilizing role in solutions containing ketorolac tromethamine and BAC. Trial Ex. SI, Ex. M, Table E; RX 1038:22-1041:10, 1193:11-1195:16.

39. Similarly, Dr. Mitra's tests showed that solutions containing 0.01% wt/vol BAC and either 0.2% or 0.25% wt/vol ketorolac tromethamine appeared hazy. Solutions containing 0.01% wt/vol BAC and 0.175%, 0.3%, or 0.35% wt/vol ketorolac tromethamine did not appear hazy to the human eye, but the spectrophotometer picked up haziness in these solutions that was not visible to the human eye, showing that a complex between BAG and ketorolac tromethamine was forming at these concentrations. The addition of Octoxynol 40 cleared all of the haziness present in all of these solutions. Trial Ex. SI at 22; R.T. 1196:21-1201:12.

40. Dr. Mitra's tests on NSAIDs other than ketorolac tromethamine showed similar results. A solution containing 0.03 % wt/vol of the NSAID flurbiprofen and 0.01 % wt/vol BAC was turbid, but the addition of 0.02% wt/vol Octoxynol 40 cleared the solution. By contrast, the addition of sodium chloride to this flurbiprofen/B AC solution, without any Octoxynol 40, did not clear the solution. Likewise, a solution containing 0.5% wt/vol of the carboxyl group-containing NSAID indoraethacin and 0.01% BAC was turbid, but the addition of 0.01% wt/vol Octoxynol 40 cleared the solution. Again, the addition of sodium chloride to this indomethacin/BAC solution, without

any Octoxynol 40, did not clear the solution. Trial Ex. SI, Ex. M., Tables J, M; R.T. 1208:1-1212:7, 1221:25-1224:6.

41. A solution containing only ketorolac tromethamine, BAC, edetate disodium, and sodium chloride, with no Octoxynol 40, will be cloudy. Specifically, Defendants admit that an aqueous solution containing only 0.5% wt/vol ketorolac tromethamine, 0.01% wt/vol BAC, 1.00 gram/liter edetate disodium dehydrate U.S.P., and 7.00 grams/liter sodium chloride U.S.P. will be cloudy. Trial Ex. 302; R.T. 1773:17-1774:3.

42. The tests of Syntex scientist Cynthia Pulsipher that used a spectrophotometer to test the light transmittance through various solutions showed an interaction between ketorolac tromethamine and BAC that resulted in decreased light transmittance. The decrease in light transmittance was dependent on the concentrations of ketorolac tromethamine and BAC. For example, in solutions containing 0,10% wt/vol and 0.05% wt/vol ketorolac tromethamine, turbidity was observed as increasing amounts of BAC were added. The addition of sodium chloride to the 0.05% wt/vol ketorolac tromethamine solution caused the turbidity problem to appear at lower concentrations of BAC. In a solution containing 0.01% wt/vol BAC, turbidity was observed as ketorolac tromethamine was added, with the turbidity lessening and eventually clearing as more ketorolac tromethamine was added. Ms. Pulsipher's tests also showed that the addition of Myrj did not solve the turbidity problem. Trial Ex. 208; R.T. 407:17-418:4.

43. Ms. Lidgate observed that formulations containing 0.01% wt/vol BAC appeared very turbid after the addition of 0.40% and 0.50% wt/vol ketorolac. On another day, Ms. Lidgate recorded that turbidity began to clear in 0.01% wt/vol BAC solutions at concentrations of ketorolac greater than 0.36% wt/vol, but a solution containing 0.01% wt/vol BAC and up to 0.6% wt/vol ketorolac was still slightly turbid. Trial Ex. 200; R.T. 688:1-694:2.

44. Dr. Fu's experiments showed that the following solutions were turbid: a solution of 0.006% wt/vol BAC and containing between 0.07% wt/vol and 0.3% wt/vol ketorolac tromethamine; a solution of 0.008% wt/vol BAC and containing between 0.07% wt/vol and 0.35% wt/vol ketorolac tromethamine; and a solution of 0.01% wt/vol BAC and containing between 0.07% wt/vol and 0.31% wt/vol ketorolac tromethamine. Dr. Fu's experiments also showed that, although 0.5% ketorolac tromethamine solutions were clear with 0.006%, 0.008%, and 0.01 % BAC at pH 7.4, such solutions became cloudy at pH's of 6.2, 6.7, and 6.2, respectively. Trial Ex. 193; R.T. 864:8-866:2, 1684:3-21.

45. Ms. Lidgate also performed tests showing that solutions containing ketorolac tromethamine, BAC, and Octoxynol 40 remained clear over time while otherwise identical solutions containing ketorolac tromethamine, BAC, and other surfactants became turbid. Specifically, solutions containing the surfactant Tween 80 became turbid when stored for one month at room temperature, at 40EC, and at a temperature cycling from 4-40EC. Solutions containing the surfactant Myrj 52 became turbid when stored for one

month at 40EC and when stored for five months at room temperature and at 40EC. By contrast, all of the solutions containing Octoxynol 40 remained clear under all storage conditions. Trial Exs. 204, 205; RX 695:1-701:14.

46. In another experiment, Ms. Lidgate showed that a higher concentration of Octoxynol 40 was better able to maintain the clarity of a ketorolac tromethamine/B AC solution than a lower concentration of Octoxynol 40. Specifically, in a solution of 0.5% wt/vol ketorolac tromethamine, 0.1% wt/vol EDTA, 0.7% wt/vol sodium chloride, and 0.01% wt/vol BAC that was stored for two months at various temperatures, aa Octoxynol 40 concentration of 0.01% wt/vol kept the solution free of particulate matter, but an Octoxynol 40 concentration of 0.005% wt/vol did not keep the solutions free of particles. Trial Ex. 107 at SYN0001308-09, SYN0001357; R.T. 891:3-894:18.

47. The addition of Octoxynol 40 to a solution of a carboxyl group-containing NS AID and BAC results in a solution that has "robust" stability because Octoxynol 40 forms micelles in the solution. These micelles include a "water-liking" outer sphere and a "water-repelling," or hydrophobic, inner portion. The formation of these micelles can prevent the interaction between the NSAID and BAC in two ways: either the NSAID and BAC are incorporated into the micelle itself, preventing the formation of a complex, or the insoluble complex is incorporated into, and solubilized in, the inner hydrophobic core of the micelle. R.T. 1686:13-1689:21, 1016:1-1017:25.

48. Octoxynol 40 adds to the "robustness" of a formulation by limiting the concentration ranges of the carboxyl group-containing NSAID and BAC at which an insoluble complex will form. Because of this effect, even large variations in, for example, temperature, quality of ingredients, or packaging will not cause the formulation to become unstable. R.T. 1689:22-1692:1. This effect is confirmed by Ms. Lidgate's tests showing that solutions containing Octoxynol 40 remained clear over time at a variety of temperatures. Trial Exs. 204, 205; R.T. 695:1-701:14.

49. Sodium chloride does not affect a solution of a carboxyl group-containing NSAID and BAC in the same manner as does Octoxynol 40. Although sodium chloride has some effect on micelle formation, it does not have the same effect as Octoxynol 40 in that it does not significantly limit the concentration ranges of NSAID and BAC at which a complex will form. The addition of sodium chloride to a solution of a carboxyl group-containing NSAID and BAC will not, therefore, lead to a robust formulation. R.T. 1662:9-1664:11.

50. Studies performed by Teresa Kuan of Allergan confirm both the existence of an interaction between ketorolac tromethamine and BAC and the role of Octoxynol 40 in minimizing that interaction and promoting solution clarity. Ms. Kuan tested formulations that included 0.4% wt/vol ketorolac tromethamine, Octoxynol 40 (tested at concentrations from 0.001% to 0.005% wt/vol), and BAC (tested at concentrations from 0.005% to 0.007% wt/vol). The solutions were stored for six months at 25°C and at 40°C. The tests confirmed that BAC and ketorolac tromethamine interact by showing that turbidity

increased in otherwise identical solutions when the concentration of BAC was increased. The tests also confirmed that Octoxynol 40 minimized this interaction between BAC and ketorolac because turbidity decreased in otherwise identical solutions when the concentration of Octoxynol 40 was increased. Trial Exs. 151, 280; R.T. 1352:10-1374:23.

51. Tests performed by a third-party contractor, Particle Technology Labs, on Novex' s ANDA formulation (a 0.5% wt/vol ketorolac tromethamine and 0.01% wt/vol BAC solution) showed that solutions containing Octoxynol 40 had significantly fewer subvisible particles than otherwise identical solutions without Octoxynol 40. Trial Ex. 186; R.T. 1509:21-1514:12.

52. Tests by another third-party contractor, Quintiles Laboratories, on 0.5% wt/vol ketorolac tromethamine ophthalmic formulations containing 0.01% wt/vol BAC, with and without Octoxynol 40, showed that, at least under certain conditions, solutions with Octoxynol 40 remained more stable over the testing period than solutions without Octoxynol 40. This was indicated by the significantly smaller increase in the number of subvisible particles in a formulation containing Octoxynol 40 that was stored in 6 mL bottles at 40°C, as compared to the same formulation without Octoxynol 40 that was stored under the same conditions. Trial Exs, 020, 023, 100, 101; R.T. 1410:24-1420:24, 1450:21-1452:24, 1455:2-1459:16.

53. Although Defendants presented evidence of certain tests by Dr. Mitra, and tests by Novex

Pharma, in which solutions of ketorolac tromethamine and BAC were found to be clear even without the addition of Octoxynol 40, those tests do not show that Octoxynol 40 has no function in the patented formulations. The Court finds that the evidence introduced by defendants failed to establish that solutions without Octoxynol 40 would be able to withstand changes in environment, pH, packaging, or quality of components. Accordingly, Defendants have failed to counter Plaintiffs' evidence that Octoxynol 40 performs a function by imparting a robust stability to solutions of ketorolac tromethamine and BAC credible.

54. Dr. Mitra did not perform tests on all carboxyl group-containing NSAIDs. In particular, Dr. Mitra did not perform any tests on diclofenac sodium or suprofen, both of which are carboxyl group-containing NSAIDs. Novex Pharma did not perform any tests on the interaction between BAC and any carboxyl group-containing NSAID other than ketorolac tromethamine. Novex Pharma also did not perform any tests on solutions containing a quaternary ammonium preservative other than BAC. R.T. 201:7-23, 202:23-203:19, 1228:6-15.

55. The tests presented by Defendants that evaluated the effect of Octoxynol 40 and/or compared the effect of Octoxynol 40 with the effects of other surfactants all used BAC and ketorolac tromethamine from a single source. Novex Pharma, in general, did not seek to determine whether the particular homolog content of the BAC that it was using was having an effect on the stability of the formulations or whether any lot-to-lot variability in the ketorolac tromethamine was having an effect On the one occasion on which Dr.

Mitra tested the effect of using different types of BAC, he found that the type of BAC used had a significant effect on the degree of complexation between ketorolac tromethamine and BAC. Similarly, a test performed by Ms. Pulsipher at Syntex confirmed that variability between lots of ketorolac tromethamine could affect the stability of the resulting formulation. Trial Ex. 209; R.T. 186:25-187:7, 196:2-200:12, 381:3-392:5, 1202:17-1207:25.

56. Defendants failed to establish that the ingredients used in the tests performed by Dr. Mitra and Novex Pharma were substantially similar to the ingredients used by the Syntex researchers at the time of the application for the '493 patent Defendants' test results evaluating the effect of Octoxynol 40 and/or comparing the effect of Octoxynol 40 with the effects of other surfactants are entitled only to limited weight due to the fact that a variety of grades, sources, or types of ingredients were not tested. Moreover, because the homolog content of the BAC used in a formulation has a significant effect on the degree of complexation between ketorolac troiDethamuie and BAC, Defendants cannot show mat the results of their tests would have been the same had a different grade of BAC been used. Likewise, Defendants cannot show that the results of their tests would have been the same had a different source of ketorolac tromethamine been used.

57. Defendant Novex Pharma applied for the right to sell two different formulations of generic Acular in Canada, one containing Octoxynol 40 and one that contained no Octoxynol 40 but that was otherwise identical. The Canadian authority rejected Defendants'

application for the formulation without Octoxynol 40. In its letter to Novex Pharma, rejecting the application, the Therapeutic Products Directorate (the Canadian equivalent of the FDA) stated:

> The surfactant Octoxynol is cited as a skin penetration enhancer (refer to D.W. Osbome and J. Henke, Pharm. Tec. November, 1977), so its role in the efficacy of the ophthalmic solution is not known. Therefore, you are requested to withdraw this formulation or provide evidence from adequate studies that the efficacy of this formulation is equivalent to the innovator's formulation.

Novex Phanna subsequently withdrew the application in the face of the rejection. Trial Exs. GA, SH: RX 74:15-76:12, 78:23-81:25.

58. Based on the evidence introduced at trial, the Court finds that, in an ophthalmic formulation, concentrations of ketorolac tromethamme within the ranges set forth in the claims of the '493 patent, and including 0.01%, 0.03%, 0.1%, 0.25%, 0.4%, and 0.5% wt/vol are effective in the treatment of ophthalmic disease. The Court also finds that ACULAR® is useful in the treatment of ophthalmic, disease caused by, associated with, or accompanied by inflammatory processes in that it aids in the treatment of allergic conjunctivitis and in the treatment of postoperative inflammation following cataract extraction.

59. The Court further finds that solutions containing ketorolac tromethamine and BAC are often

visibly cloudy and turbid within the ranges of ketorolac trometharaine that are effective in the treatment of ophthalmic disease. In addition, even solutions of ketorolac tromethamine and BAC that are not visually cloudy have been shown to contain invisible particulate matter. Octoxynol 40 has been shown to be useful at least in helping to prevent turbidity, cloudiness, and the formation of particles in solutions of ketorolac tromethamine and BAC within the ranges of ketorolac tromethamine that are effective in the treatment of ophthalmic disease.

60. The Court finds that Octoxynol 40 performs a useful function in the compositions, methods of treatment of ophthalmic disease, and preservative systems claimed in Claims 1-16 of the '493 patent Octoxynol 40 is useful in helping to prevent the formation of a complex between BAC and ketorolac tromethamine in formulations within the claims of the '493 patent, thus helping to maintain the clarity and antibacterial efficacy of those formulations. Octoxynol 40 is also usefiil in reducing the number of particles in formulations of ketorolac tromethamine and BAC at concentrations within the claims of the '493 patent. Octoxynol 40 performs a useful function in the formulations, methods of treatment, and preservative systems claimed in Claims 1- 16 of the '493 patent by imparting robustness to the claimed formulations, thus allowing the formulations to withstand larger changes in environment, pH, packaging, and quality or composition of ingredients man would be possible without Octoxynol 40.

CONCLUSIONS OF LAW

61. A patent is presumed to be valid under 35 U.S.C. § 282. This presumption attaches to each claim independently of the other claims of the patent *See Jones* v. *Hardy,* 111 F.2d 1524, 1528 (Fed. Cir. 1984). The patent challenger must establish facts demonstrating invalidity by clear and convincing evidence, and the ultimate burden of persuasion never shifts away from the patent challenger. *See id* "'Clear and convincing' evidence has been described as evidence which produces in the mind of the trier of fact an abiding conviction that the truth of a factual contention is 'highly probable.'" *Price* v. *Symsek,* 988 F.2d 1187, 1191 (Fed. Cir. 1991). The patentee responding to a validity challenge need only submit sufficient evidence to rebut any proof of invalidity offered by the challenger, and when the challenger fails to identify any persuasive evidence of invalidity, the very existence of a patent satisfies the patentee's burden on the validity issue. *See Canon Computer Systems, Inc.* v. *Nu-Kote International, Inc.,* 134 F.3d 1085, 1088 (Fed. Cir. 1998).

62. 35 U.S.C. § 101 provides, in relevant part:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter... may obtain a patent therefor, subject to the conditions and requirements of this title.

63. The first step in analyzing the utility of the claimed inventions is to construe the claims. *See Raytheon Co.* v. *Roper Corp.*, 724 F.2d 951, 956 (Fed. Cir. 1983) ("In determining utility, ... the claims must first be interpreted to define the invention to be tested for utility."). The second step is to examine the utility of the claimed invention. "Assessing utility requires interpreting the claim in order to define the invention and then testing the invention for utility." *Ares-Serono, Inc.* v. *Organon International B.V.*, 862 F. Supp. 603, 607 (D. Mass. 1994). As the final step in the analysis, the court must determine whether it has been proved, by clear and convincing evidence, that the claimed inventions are *"totally incapable* of achieving a useful result" *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992) (emphasis added). "The threshold of utility is not high: An invention is "useful" under section 101 if it is capable of providing some identifiable benefit" *Juicy Whip, Inc.* v. *Orange Bang, Inc.*, 185 F.3d 1364,1366 (Fed. Cir. 1999). "When a properly claimed invention meets at least one stated objective, utility under § 101 is clearly shown." *Raytheon*, 724 F.2d at 958.

64. The Manual of Patent Examining Procedures ("MPEP") reinforces the fact that utility must be evaluated on the basis of the invention as claimed: "to satisfy the requirements of 35 U.S.C. § 101, an applicant must claim an invention that is statutory subject matter and must show that the *claimed invention* is 'useful' for some purpose either explicitly or implicitly." MPEP § 2107.01 (emphasis added); *see also id.* § 2107.02(H) ("Upon initial examination, the examiner should review the

specification to determine whether there are any statements asserting that the claimed invention is useful for any particular purpose.").

65. The formulations, preservative systems and methods of using those formulations claimed in the '493 patent meet the stated objective, as set forth in the specification, of treating eye inflammation caused by a variety of diseases, as evidenced by (1) Defendants' infringement of the claims of the '493 patent; (2) the FDA's approval of ACULAR® and Allergan's 0.4 % ketorolac tromethamine solution; (3) the commercial success of ACULAR®; (4) Defendants' copying of ACULAR® and corresponding certification to the FDA that Defendants' generic version of ACULAR® is safe and efficacious in the treatment of ophthalmic disease; and (5) the fact that animal and clinical studies conducted by Syntex researchers prior to filing the NDA for ACULAR® showed that the patented formulations and methods were efficacious at reducing swelling, eye irritation, and other inflammation symptoms in the eye.

66. The Federal Circuit has held that 'infringement of otherwise valid claims mandates *as a matter of law* a finding of utility." *Raytheon,* 724 F.2d at 959 (emphasis added). This is because "[p]eople rarely, if ever, appropriate useless inventions." *Id.; see also E.I. du Pont de Nemours & Co. v. Berkley & Co., Inc.*, 620 F.2d 1247, 1258-59 (8th Cir. 1980) (stating that it is "axiomatic" that "one who appropriates the teachings of a patent may not deny the utility of the invention" and holding that the defendant's infiingement was "an admission of utility in the invention"); *Tapco Products Co.* v. *Van Mark Products*

Corp., 446 F.2d 420, 428 (6th Cir. 1971) (holding that because the defendants "have copied, virtually exactly, plaintiff's bending brake," "defendants may not challenge the utility of the Hat surfaces which plaintiff claims as its invention"). Therefore, Defendants' infringement of the claims of the '493 patent demonstrate the utility of the claimed inventions.

67. Furthermore, to secure FDA approval, a drug manufacturer must demonstrate that the drug is safe and effective for each of its intended uses. *See* 21 U.S.C. § 355(d). The standards under Section 355(d) are "strict and demanding." *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 619 (1973). "The FDA may not approve an NDA unless, inter alia, it has substantial evidence of the safety and efficacy of the drug in question." *Hoffmann-La Roche, Inc.* v. *Harris*, 484 F. Supp. 58, 60 (D.D.C. 1979). Moreover, the FDA may always withdraw its approval if the drug is subsequently discovered to be unsafe or ineffective. "[I]f [the drugs] were not safe and effective, FDA would presumably have exercised its power and performed its duty to withdraw approval of them." *Id.* at 61.

68. The fact that the FDA has approved ACULAR® and Allergan's 0.4 % ketorolac tromethamine solution as safe and effective is proof of the usefulness of the claimed formulations under 35 U.S.C. § 101. The Federal Circuit has held that the "utility" of a drug under Section 101 is established long before the FDA approves the drug for sale:

> Usefulness in patent law, and in particular in the context of

> pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.

In re Brana, 51 F.3d 1560, 1568 (Fed. Cir. 1995).

69. The MPEP agrees; in discussing (he utility inquiry appropriate for an application on a drug approved by the FDA for trials, but that has not yet been approved for sale, the MPEP states: "If the [FDA] reviewed use is one set form in the specification, [Patent] Office personnel must be extremely hesitant to challenge utility. . . Thus, in challenging utility* Office personnel must be able to carry their burden that *there is no sound rationale for the asserted utility even though experts designated by-Congress to decide the issue have come to an opposite conclusion."* MPEP § 2107.03(V) (emphasis added).

70. In sum, the FDA's approval of ACULAR® and Allergan's 0.4 % ketorolac tromethamme solution as safe and "effective" necessarily means that the formulations and methods of treatment of the '493 patent are "useful" under 35 U.S.C. § 101.

71. Courts have also recognized that the commercial success of an invention that incorporates the features claimed in a patent evidences the utility of the claimed invention. *See Raytheon,* 724 F.2d at 959. Syntex's invention of the 0.5% ketorolac tromethamine solution, manufactured and distributed by AHergan as ACULAR®, has been met with great

commercial success. As of the end of 2001, Allergan had made over $291 million in net sales of ACULAR®. Because ACULAR® embodies the inventions claimed in the '493 patent, ACULAR®'s commercial success is further evidence of the usefulness of the inventions of the '493 patent.

72. Defendants' copying of Plaintiffs' patented inventions is further evidence of the usefulness of the invention at issue as is Defendants' certification to the FDA that their generic version of ACULAR® is safe and efficacious in the treatment of ophthalmic disease. Also significant is the fact that Defendants' copying followed the inventions' commercial success. "Generally, '[commercial success is strong evidence of utility and patentability... and where followed by defendants copying the patented device as closely as possible ... is sufficient to establish utility.'" *Wilden Pump & Engineering Co.* v. *Pressed & Welded Products Co.*, 655 F.2d 984, 988 (9th Cir. 1981) (quoting A. Deller, 1 Deller's Walker on Patents § 87 at 497 (2d ed. 1965)). The Federal Circuit has also recognized that "lack of utility cannot co-exist with infringement and commercial success." *Raytheon*, 724 F.2d at 959 (holding patented invention not invalid for lack of utility due to evidence of Defendants' copying of the invention and commercial success).

73. Plaintiffs' numerous animal and clinical studies show that ketorolac tromethamme ophthalmic solutions effectively right inflammation in mammals and humans. Data from the animal studies show the utility of the claimed formulations by demonstrating that ketorolac tromethamine ophthalmic formulations are useful to treat ophthalmic diseases when applied to

the eye. In addition, the clinical studies have established the utility of the formulations and treatment methods claimed in the '493 patent hi treating ophthalmic diseases in humans.

74. In light of the evidentiary record, when the patented formulations are viewed as a whole, the Court finds that the formulations and methods of treatment claimed in the '493 patent are "useful" in treating ophthalmic disease. Defendants do not attempt to argue to the contrary and therefore have not proved by clear and convincing evidence that the patented formulations and methods of treatment lack utility.

75. While this Court stated in its Claims Construction Order "that the improvement over the prior art contained in the 493 patent is the use of Otoxoynol 40 as a surfactant, as the patent itself teaches... Therefore, if 040 does not perform this stabilizing function, as defendants argue, the patent is invalid", the Court finds that the record here establishes that Octoxynol 40 serves a useful stabilizing function in the patented formulations, preservative systems, and methods of using those formulations. Moreover, a combination claim, such as the claims of the '493 patent, covers the combination as a whole. *See Aro Manufacturing Co., Inc. v. Convertible Top Replacement Co., Inc.*, 365 U.S. 336, 344-45 (1961) ("[I]f anything is settled in the patent law, it is that the combination patent covers only the totality of the elements in the claim and that no element, separately viewed, is within the grant").

76. Defendants' arguments regarding the functionality of Octoxynol 40 in Plaintiffs' patented formulations do not compel a different conclusion where, as here, Defendants still have not proved by clear and convincing evidence that Octoxynbl 40 lacks utility. This conclusion follows because in order for a patent claim to be invalid due to lack of utility, the claimed invention "must be *totally incapable* of achieving a useful result," *Brooktree,* 977 F.2d at 1571 (emphasis added), and must have no *"identifiable benefit" Juicy Whip,* 185 F.3d at 1366 (emphasis added). In the absence of clear and convincing evidence that Octoxynol 40 has no identifiable benefit and is totally incapable of achieving a useful result in the patented formulations and methods of use the Court rejects Defendants challenge on this ground.

77. To the extent that Defendants maintain that the functionality of Octoxynol 40 must be evaluated only across certain "ophthalmologically acceptable" concentration ranges of ketorolac tromethamine and BAC, Defendants are misconstruing the import of the phrase "ophthahnologically acceptable" as used in the claims. Contrary to Defendants' position, the Court agrees with Plaintiffs mat the term "ophthalmologically acceptable" does not define the concentration ranges of the various ingredients in the patented formulations, but rather defines the *type of drug* to be used in the formulations.

78. Moreover, the use of the term "ophthalmologically acceptable" in the preambles of some of the claims does not serve as a claim

Limitation.[7] "It is well settled that "[i]f fte body of the claim sets out the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation."" *Schumer v. Laboratory Computer Systems, Inc.*, 308 F.3d 1304, 1310 (Fed. Cir. 2002) (quoting *Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1373-74 (Fed. Cir. 2001)); *see also Bristol-Myers Squibb Co.* v. *Immunex Corp.*, 86 F. Supp. 2d 447, 451 (D.N.J. 2000) (holding mat a "shorthand encapsulation of the advantages of the invention" in the preamble does not constitute a claim limitation); *SIX, Inc.* v. *Brine, Inc.*, 37 F. Supp. 2d 740,752 (D. Md. 1999) (same).

79. In this case, the "complete invention" is set forth in the bodies of the claims. The bodies of the claims describe, in detail, the different components to be used to make the patented formulations; the preambles do nothing more than simply reiterate certain terms, including "ophthalmologically acceptable," that are already used in the bodies of the claims. The preambles are not necessary to give "life, meaning and vitality" to the claims, and the language of the preambles is therefore superfluous.

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[7] The preambles of Claims 8-14 do not even include the term "ophthalmologically acceptable therefore, even if that term were construed as a limitation on the concentrations of ingredients in the patented formulations, that limitation does not apply to Claims 8-14.

80. The concentration ranges of the ingredients in the patented formulations are defined by the terms "effective amount" and "antimicrobially effective amount." Defendants presented no evidence regarding the amounts of the various ingredients that are "effective" or "antimicrobially effective" and did not attempt to contradict Plaintiffs' evidence that concentrations of ketorolac tromethamine as low as 0.01% wt/vol are effective in the treatment of ophthalmic disease.

81. Defendants also argue that all of the '493 patent claims are invalid because Octoxynol 40 is not necessary to achieve a clear, "ophthalmologically acceptable" formulation, defined by Defendants to require NaCl (table salt), disodium edetate, and enough hydrochloric acid (HCl) or sodium hydroxide (NaOH) to adjust the pH of that solution to be nearly neutral (pH 7.0). Besides the fact that, as explained above, "ophthalmologically acceptable" defines only the type of drug used in the formulation and not the characteristics of the formulation, this argument fails for the additional reason that Claims 1-4, 8-11, and 15-16 do not even claim pH, salt, or EDTA, and Claims 5 and 12 do not claim salt or EDTA. The term "ophthalmologically acceptable" in the preambles of some of these claims does not import the requirements of a neutral pH, NaCl, and EDTA not present in language of the claims. Likewise, the term "ophthalmologically acceptable" in the preambles of Claims 6 and 7 cannot modify the explicit pH and concentrations of NaCl and EDTA claimed in those claims.

82. Moreover, even if the functionality of Octoxynol 40 were the proper focus of the utility inquiry *and* the patents reference to the term "ophthalmologically acceptable" were construed to define the characteristics of the patented formulations, Defendants have not met their burden of demonstrating that Octoxynol 40 is "totally incapable" of achieving a useful result in the patented formulations,

83. The relevant test results show that Octoxynol 40 performs a useful, stabilizing function in the patented formulations. Test data accumulated by scientists at Syntex and Allergan, and by outside laboratories, shows that the key ingredients of the '493 patent formulations "ketorolac tromethamine and BAC'are incompatible and that Octoxynol 40 consistently helped to maintain the stability of formulations containing these two key ingredients at a variety of concentrations and conditions" including those that Defendants would deem to be "ophthalmologically acceptable." The Court finds on this record that Octoxynol 40 helped to impart a "robust" stability to the formulations.

84. Defendants' expert's test results comparing the effects of other surfactants, such as polysorbate 80, in clearing turbidity with the effect of Octoxynol 40 do not support a finding of invalidity. It is well established that "[a]n invention need not be the best or the only way to accomplish a certain result" *Stiftung v. Renishaw PLC,* 945 F.2d 1173, 1180 (Fed. Cir. 1991).

85. Defendants' test results evaluating the effect of Octoxynol 40 and/or comparing the effect of Octoxynol 40 with the effects of other surfactants are entitled only to limited weight due to the fact that a variety of grades, sotirces, or types of ingredients were not tested. Moreover, because the homolog content of the BAC used in a formulation has a significant effect on the degree of complexation between ketorolac tromethamine and BAC, Defendants cannot show that the results of their tests would have been the same had a different grade of BAC been used. Likewise, Defendants cannot show that the results of their tests would have been the same had a different source of ketorolac tromethamine been used. Finally, Defendants cannot show mat the results of their tests would have been same had all carboxyl group-containing NSAIDs or all quaternary ammonium preservatives been tested.

86. Defendants' test results are also entitled only to limited weight because defendants failed to establish bdnantthere was no evidence introduced that the ingredients used in those tests were substantially similar to the ingredients used by the Syntex researchers at the time of the application for the '493 patent Utility of an invention is determined as of the date of tiling of the patent application. *See In re Brana,* 51 F.3d at 1567 n. 19. Therefore, the Court accords only limited weight to the results of tests that used ingredients that may have been different from those available at the time of the patent application.

87. Even if Octoxynol 40 were not needed at certain concentrations of B AC and ketorolac tromethamine, that would not be sufficient to

invalidate the claims of the '493 patent. In order to meet the utility standard, Octoxynol 40 does not have to be useful *all* the time or under *all* conditions; "the fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp.* v. *Al George, Inc.*, 730 F.2d 753, 762 (Fed. Cir. 1984); *see also United States Ordnance Co.* v. *United States*, 85 Ct. Cl. 563 (Ct. Cl. 1937) ("The fact that a device works imperfectly or occasionally fails entirely does not necessarily make a patent upon it invalid."). The requirement of utility is satisfied if the claimed invention is "useful to *some extent* and in certain applications." *Stiftung*, 945 F.2d at 1180 (emphasis added).

88. Finally, Defendants make an alternative lack of utility argument that is unrelated to the functionality of Octoxynol 40 in the patented formulations: they argue that the patented formulations lack utility because they are not useful across the entire range of ketorolac tromethamine and BAC concentrations that are claimed. An invention meets the utility requirement, however, as long as it is "useful to *some extent* and in certain applications." *Stiftung*, 945 F.2d at 1180 (emphasis added). The Federal Circuit addressed a situation similar to this one in *Envirotech Corp.* v. *Al George, Inc*, 730 F.2d 753, 762 (Fed. Cir. 1984). In that case, the accused infringers argued lack of utility based on the contention that a graph contained in the patent did not accurately represent "the desired operating conditions described in the patent." *Id.* at 761. The court found that what the accused infringers were actually trying to argue was that the specification failed to disclose

adequately "how to use" the invention without undue experimentation; the court noted that a lack of utility defense is appropriate only "when there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention." *Id.* at 762. The court went on to state:

> Even if Defendants' argument of inadequate experimentation or inexact correlation were to apply, the fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility.

Id. Similarly, in this case, Defendants have not shown a lack of utility based on the necessity for some routine experimentation in order to determine the appropriate concentration ranges of certain ingredients. Furthermore, even if some portion of the concentration ranges set forth could not be used to meet the objectives set forth in the patent, such a finding of "limited utility" does not invalidate the patent. Moreover, Defendants' citation to *In Re Corkhill,* 771 F.2d 1496, 1501 (Fed. Cir. 1985) does not support a different conclusion on this record.

89. As established by the findings of fact set forth in paragraphs 26 through 60, Defendants have failed to prove by clear and convincing evidence that any claim of the '493 patent is invalid due to lack of utility.

IV. ENABLEMENT
FINDINGS OF FACT

90. The specification of the '493 patent sets forth four example formulations (Examples 1 through 4) that list the identity and concentration of each of the ingredients in the example formulations. The preferred solution is set forth in column 5 of the specification of the '493 patent and contains 0.50% wt/vol ketorolac tromethamine and 0.02% wt/vol of a 50% aqueous solution of BAC.

91. The specification of the '493 patent indicates that the inventions of the patent may be used in mammals, not just humans. The word "treatment" is defined to include "treatment of any disease in a mammal." '493 patent, column 2, line 61.

92. The concentrations of the quaternary ammonium preservatives BAC, Cetrimide, and CPC that could safely be used in an ophthalmic formulation were commonly known to persons of ordinary skill in the field of pharmaceutical formulations at the time of the invention. In particular, it was well-known that a BAC concentration of 0.01% wt/vol was safe. R.T. 981:1-989:8; 1133:8-1136:19.

93. Studies to determine how much of an active ingredient to use in a particular drag formulation, referred to as dose-response studies, are routinely used in the pharmaceutical industry. R.T. 1276:20-1278:12.

94. There was no evidence introduced that any experimentation that would have been necessary

in order to establish appropriate concentrations for the ingredients of the patented formulations would not have been experimentation routine to a person of ordinary skill in the art of ophthalmic formulations.

95. Defendants have introduced no evidence related to the concentrations of ingredients that could be used in non-human mammals. Therefore, Defendants have introduced no evidence as to whether the '493 specification is enabling as to the treatment of animals.

CONCLUSIONS OF LAW

96. 35. U.S..C. § 112, paragraph 1 provides:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such rail, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out Ms invention.

97. Invalidity for lack of enablement is a conclusion of law that must be supported by facts proved by clear and convincing evidence. *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990). "A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the

disclosure in the patent document, could make and use the invention without undue experimentation. It is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification." *Id,* Furthermore, "a patent need not teach, and preferably omits, what is well known in the art" *Hybritech Inc.* v. *Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1384 (Fed. Cir. 1986). Even "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988) (quoting *In re Jackson,* 217 U.S.P.Q. 804, 807 (Bd. App. 1982)).

98. Defendants first contend mat the '493 patent claims are not enabled because they are not "useful." As explained above, however, Plaintiffs* inventions are useful and Defendants have failed to meet their burden of proof that they are not. Because the determinations of enablement and usefulness are closely related inquiries, Defendants' argument that the claims of the '493 patent are not enabled because they are not useful fails along with, their non-utility defense. *See, e.g., Raytheon,* 724 F.2d at 959-60 (reversing holding of lack of enablement after reversing finding of lack of utility, as the two defenses "rest[ed] on the same foundation").

99. Defendants' next argument is that each claim of the '493 patent, is invalid under paragraph 1 of 35 U.S.C. § 112 because quaternary ammonium preservatives are claimed in the range of 0.001%-l .0% wt/vol but are unsafe in concentrations above 0.2%

wt/vol. This argument does not apply, however, to Claims 6,7,13, and 14 because these claims are limited to I formulations that contain 0.02% wt/vol of a 50% solution of BAC, in other words, 0.01% wt/vol BAC. These claims therefore claim an exact, admittedly safe amount of BAC.

100. Furthermore, the disclosure in the '493 patent would have, at the time of the invention, reasonably apprised a person skilled in the art of how to make and use Plaintiffs' inventions without undue experimentation. As Dr. Mitra himself explained, the concentrations of BAC, Cetrimide, and CPC that could safely be used in an ophthalmic formulation were commonly known to persons of ordinary skill in the field of pharmaceutical formulations at the time of the invention.

101. Defendants next argue that each claim of the '493 patent is invalid for lack of enablement because the "ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug" is claimed in me range of 0.001%-10.0% wt/vol but cannot be tolerated by the eye at concentrations above 1.0% wt/vol. Dose-response studies, however, are routinely used in the pharmaceutical industry to determine how much of an active ingredient to use in a particular drug formulation, and there was no evidence introduced that one of ordinary skill in the art would not have known how to use such a study to select the appropriate concentration of drug to use.

102. Finally, the specification of the '493 patent is enabling because the method of use claims of the '493 patent, Claims 8-14, cover use by "mammals,"

not just humans. Therefore, the range of concentrations claimed for the quaternary ammonium and NSAID compounds is not limited to just those concentrations that would have been approved by the FDA. There was no evidence introduced that an ordinary formulator at the time of the invention would not have been able to choose an appropriate concentration range without undue experimentation depending on the intended recipient of the formulation.

103. As established by the findings of fact set forth in paragraphs 90 through 95, Defendants have failed to prove by clear and convincing evidence that any claim of the '493 patent is invalid under 35 U.S.C. § 112, paragraph 1 due to lack of enablement.

V. INDEFINITENESS
FINDINGS OF FACT

104. There was no evidence introduced and there is no evidence in the record that one of ordinary skill in the art of ophthalmic formulations would not understand the scope of any of the claims of the '493 patent, read in light of the specification.

105. To the extent that Defendants' argue indefiniteness based upon the facts which support their argument of invalidity due to lack of utility and enablement, the Court incorporates its previous findings of fact/law regarding utility and enablement and, as such, rejects Defendants' assertion that the 493' patent is invalid for indefiniteness.

CONCLUSIONS OF LAW

106. 35. U.S.C. § 112, paragraph 2 provides:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

107. "Whether a claim is invalid for indefiniteness depends on whether those skilled in the art would understand the scope of the claim when the claim is read in light of the specification." *North American Vaccine, Inc. v. American Cyanamid Co.*, 7 F.3d 1571, 1579 (Fed. Cir. 1993).

108. Defendants' first indefiniteness argument that the claims are indefinite because they claim a "stabilizing" amount of Octoxynol 40" is duplicative of Defendants' argument concerning the operability or utility of Octoxynol 40 in the claimed formulations. The issue of operability, however, is irrelevant to the issue of indefiniteness. The Federal Circuit has held that whether claims describe an operable invention is irrelevant to definiteness under § 112(2) because "[t]he invention's operability may say nothing about a skilled artisan's understanding of the bounds of the claim." *Miles Laboratories, Inc.* v. *Shandon Inc.*, 991 F.2d 870, 875 (Fed. Cir. 1993).

109. Defendants' second inderMteness argument is that the claims are indefinite because they claim ketorolac tromethamine and BAC outside of the "ophthalmologically acceptable" ranges. As discussed above, however, the term "ophthalmologically acceptable" does not serve to define the concentration ranges of ingredients in the patented formulations, but simply defines the type of drug used in the formulations. Furthermore, [8]it is well-established that a claim is not invalid for indefiniteness simply because it is broad. *See Application of Johnson*, 558 F.2d 1008, 1016 n.17 (C.C.P.A. 1977) ("[U]ndue breadth is not indefiniteness."). Accordingly, that Plaintiffs may have claimed a broad concentration range of ketorolac tromethamine and BAC has nothing to do with indefiniteness.

110. "The law is clear that "[i]f the claims, read in the light of the specification[s] reasonably apprise those stilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more."" *North American Vaccine*, 7 F.3d at 1579-80 (quoting *Shatterproof Glass Corp. v. Libbey-Owens Ford, Co.*, 758 F.2d 613, 624 (Fed. Cir. 1985)). The specification of the '493 patent states that the claimed inventions relate to ophthalmic formulations. It also specifically states that "[t]he amount of active ingredient will vary with the particular formulation and the disease state for which it is intended," and specifies mat the ranges provided for the active

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[8] Defendants' enablement argument resting on the same contentions is addressed in Section IV, *supra*.

ingredient 'and the preservative are "approximate ranges." '493 patent, column 3, lanes 33-41. The claims of the '493 patent, read in light of the specification, would have sufficiently apprised a person of ordinary skill in the art of the scope of the claims.

111. As established by the findings of fact set forth in paragraphs 104-105, Defendants have failed to prove by clear and convincing evidence that any claim of the '493 patent is invalid under 35 U.S.C. § 112, paragraph 2 due to indefiniteness.

VI. OBVIOUSNESS
FINDINGS OF FACT

112. The '493 patent issued on May 5,1992 from Application No. 07/624,027, which was filed on December 7,1990 and which was a continuation of Application No. 07/096,173, filed on September 11,1987. The joint inventors of the '493 patent are Dr. Fu and Ms. Lidgate.

113. An Information Disclosure Statement ("IDS") was filed along with both applications, identifying the following prior art: 4,087,539 (1978) Muchowski et al; 4,089,969 (1978) Muchowski et al; 4,097,579 (1978) Muchowski et al; 4,232,038 (1980) Kluge et al; j 4,336,151 (1982) Like et al.; 4,336,152 (1982) Like et al.; 4,545,151 (1984) Waterbury; "Influence of $(Ethoxy)_5$ Octyl Phenol on the Antibacterial Properties of Preservatives," M.T. Nadir, et al., *Journal of Pharmacy and Pharmacology,* Volume 29, Supplement, December 1977, page 67P; "Ocufen (flurbiprofen sodium) 0.03% Liquifilm sterile ophthalmic solution, Allergan, product description

sheet, one page. In addition, the examiner cited the following references in initially rejecting certain claims of the '493 patent raider 35 U.S.C. § 103: 4,087,538 (1978) Portnoff; 4,230,724 (1980) Cooper et al.; 4,474,751 (1984) Haslam et al.; 4,474,811 (1984) Masuda et al.; 4,500,538 (1985) Woltersdorf; 4,559,343 (1985) Han et al.; 4,607,038 (1986) Ogata.et al.; Japanese Ref. No. 23,318 (1985); 4,349,563 (1982) Gilbert et al.; *The Condensed Chemical Dictionary,* Seventh Ed.; *McCutcheon 's "Emulsifiers and Detergents* " (1982); 'The Synergistic Effects of Nonionic Surfactants Upon Cationic Germicidal Agents," Schmolka (1973). Trial Exs. 024 at SYN0000245-48, 035 at SYN0000034-44, SYN0000050-52.

114. At trial Defendants asserted only that the combination of U.S. Patent No. 4,545,151 to Waterbury, U.S. Patent No. 4,349,563 to Gilbert et al., and U.S. Patent No. 4,559,343 to Han et al. rendered obvious the claims of the '493 patent All of the prior art references asserted by Defendants at trial were before the examiner of the application for the '493 patent.

115. A person of ordinary skill in the art at the time of the invention-is a person having a Bachelor's or Master's degree in the pharmaceutical sciences and having three to five years of experience working in the field under the supervision of a person having a Ph.D. in the pharmaceutical sciences. R.T. 1707:11-24.

116. U.S. Patent No. 4,454,151 to Waterbury (the "'151 patent" and/or the "Waterbury patent") defines a number of non-steroidal anti-inflammatory drugs ,that were found to be efficacious in the

treatment of inflammatory diseases. The '151 patent does not discuss the concepts of long-term stability or anti-microbial effectiveness and does not discuss any problem of interaction or complexation between BAC and ketorolac tromemamine". It also does not discuss the use of EDTA or any other chelating agent. Trial Ex. 004; R.T. 1158:1-16, 1159:25-1160:3 (Dr. Mitra), 1707:25-1710:6 (Dr. Stella).

117. The only example formulation in the' 151 patent, Example 1 ("Composition of Ophthalmic Solutions for topical Administration to the Eye"), does not include a surfactant in its composition. In fact, the '151 patent teaches away from the use of Octoxynol 40 in a pharmaceutical formulation in that the only time that a surfactant is mentioned, the surfactant is polysorbate 80. Trial Ex. 004; R.T. 1158:17-1159:17 (Dr. Mitra), 1709:4-1710:6 (Dr. Stella).

118. U.S. Patent No. 4,349,563 to Gilbert discusses non-steroidal anti-inflammatory drugs. The Gilbert patent does not, however, mention ketorolac tromethamine or Octoxynol 40. Moreover, the Gilbert patent teaches away from the use of a surfactant because it states explicitly that a stabilizer is not preferred. The patent also teaches away from the use of Octoxynol 40 specifically because, in the only example in the patent in which an NSAID, BAC, and a surfactant are used together, the surfactant is Tween 80. Trial Ex. WJ; R.T. 1161:13-1163:4 (Dr. Mitra), 1710:7-1712:7 (Dr. Stella).

119. U.S. Patent No. 4,559,343 to Han, et al. discloses that the addition of xanthines, such as caffeine, to ophthalmic solutions of acidic NS AIDs

helps to reduce the irritation associated with the NSADDs. The examples of the Han patent disclose the use of NSAIDs with either BAC or thimerosal and either Pluronic F127 or tyloxapol. Neither Pluronic F127 nor tyloxapol are Octoxynols, and the Han patent therefore teaches away from the use of Octoxynol 40. The Han patent further teaches away from formulations without xanthines because xanthines are set forth as necessary to a successful product. Trial Ex. AK; R.T. 1163:5-1164:21 (Mitra), 1712:8-1713:17 (Stella).

120. *McCutcheon's "Emulsifiers and Detergents"* (1982) is a directory of a large number of emulsifiers and detergents. It describes Igepal CA-897 (Octoxynol 40) as an emulsifier and a stabilizer. The use of the term, "stabilizer" in McCutcheon's has a different meaning than its use in the context of the '493 patent. *McCutcheon's* makes no mention of the use of Octoxynol 40 in pharmaceuticals in general, or in ophthalmic formulations specifically, and it makes no reference to the prevention of precipitate formation, the chemical stabilization of an unstable drug, or the maintenance of preservative action. *McCutcheon's* specifies that the primary use of Igepal CA-897 (Octoxynol 40) is for "vinyl acetate and acrylate polymerization, dying assistant, emulsifier for fats and waxes." Trial Ex. AL; R.T. 1713:18-1715:4.

121. *The Condensed Chemical Dictionary* defines "tyloxapol" as an "oxyethylated tert-octylphenolpolymethylene polymer, an essentially nontoxic, non-ionic surfactant." Tyloxapol is not an Octoxynol. The Dictionary does not specify that tyloxapol may be used as a stabilizer in an ophthalmic

solution, Tyloxapol is not included in the formulations claimed in the '493 patent Trial Ex. NK; R.T. 1715:5-16.

122. None of the prior art references cited by Defendants mention Octoxynol 40, except for *McCutcheon 's.* Defendants' expert, Dr. Mitra, provided no testimony at all regarding *McCutcheon 's,*

123. The Court finds, based on the evidence, that there would have been no motivation for one of ordinary skill in the art to combine the teachings of any of the references cited by Defendants. R.T. 1715:17-1716:2.

124. Significantly, Defendants have not identified any prior art reference that either discloses or suggests (a) that Octoxynol 40 be used in a drug formulation and/or that it be used in an ophthalmic formulation; (b) that it be used in a preservative system with a quaternary ammonium preservative; (c) that it be used in a formulation with a quaternary ammonium preservative, such as BAC; (d) that it be used in a formulation with a carboxyl group-containing NSAID, such as ketorolac tromethamine; (e) that it be used to prevent the formation of a complex between a carboxyl group-containing NSAID and a quaternary ammonium preservative; or (r) that it would act to maintain the antimicrobial effectiveness of a quaternary ammonium preservative, such as BAC, in an ophthalmic formulation.

125. There was no evidence introduced that the more detailed inventions of the dependent claims of me '493 patent, which claim specific formulations

containing specific ingredients in specific amounts, would have been obvious to a person of ordinary skill in the art at the time of their invention.

126. No pharmaceutical formulation other than ACULAR® has ever included Octoxynol 40. R.T. 1165:3-14.

127. Syntex's formulation work on a ketorolac tromethamine ophthalmic solution was begun in July of 1982 by Dr. Fu. Between July of 1982 and March of 1984, Syntex researchers mixed and tested ophthalmic solutions of ketorolac tromethamine and BAC that exhibited turbidity or cloudiness either upon mixing or after stability testing. Ms. Pulsipher described the problem of turbidity in solutions of ketorolac tromethamine and BAC as the most frustrating problem that she encountered at Syntex. In order to solve the problem, between July of 1982 and March of 1984, Ms. Pulsipher tried using various surfactants, including Myrj 52, Tween 20, Tween 80, Tetronic 1304, Pluronic F127, and Pluronic F168. None of these surfactants solved the problem because they were unable to keep a solution of ketorolac tromethamine and BAC stable under varied conditions. R.T. 338:11-20, 341:7-343:17, 350:5-375:15, 435:5-436:22.

128. In 1994, within one year of ACULAR®'s entry into the ophthalmic anti- inflammatory market, ACULAR®'s net sales were over $18 million. In 1995, ACULAR®'s net sales rose to over $21 million, and by 1999, its net sales had risen to over $46 million, hi 2001, ACULAR®'s net sales were over $58 million. All told, during the period from ACULAR®'s introduction in 1993 through 2001, ACULAR® garnered over $291

million in net sales and captured a 36.1% market share among ophthalmic anti-inflammation drugs. Trial Exs. 090,091; R.T. 1541:13-1555:11, 1558:23-1562:18.

129. ACULAR®, and its use in treating ophthalmic diseases, embodies each of the claims of the '493 patent ACULAR® is the preferred embodiment set forth in the specification of the '493 patent. Claim 7 of the '493 patent is coextensive with ACULAR®, covering nothing other than ACULAR® and any copy of it.

130. In contrast with ACULAR®'s success, ACULAR®'s chief competitor drug, Voltaren, appeared in the marketplace three years prior to ACULAR® and yet has not achieved the success of ACULAR®. Trial Exs. 091,095; R.T. 1561:20-1562:18.

131. The multi-dose aspect of ACULAR®, which is conferred by the use of BAC as a preservative, has contributed greatly to its commercial success. This is evidenced by the fact that ACULAR® has performed far better in the market than Acular PF®, which does not contain a preservative and does not contain Octoxynol 40. Trial Ex. 095; R.T. 1562:19-1566:12.

132. Allergan entered into an exclusive distribution arrangement with Syntex for the 0.5% ketorolac tromethamine ophthalmic fommlation on October 22, 1990, before the '493 patent issued. AUergan has paid to Syntex more than $133 million in royalties under this agreement Trial Exs. 083, 084; R.T. 1537:20-1540:24.

133. Plaintiffs have presented evidence that the presence of Octoxynol 40 in the patented formulations produced unexpected results, in that the formulations were stable as compared to formulations that contained other surfactants disclosed in the prior art. Ms. Lidgate generated test results that were submitted to the PTO and that unequivocally showed that formulations containing Octoxynol 40 were clear even under conditions under which formulations containing other Octoxynols, Myrj 52, or Tween 80 were turbid. Included in these results was a showing that Octoxynol 40 produced better results thaTi the closest prior art cited by the examiner, Octoxynol 5. Trial Exs. 009,024 at SYN0000280, 035 at SYN0000057-64; R.T. 761:2-762:9, 769:11-770:25.

CONCLUSIONS OF LAW

134. 35. U.S.C. § 103(a) provides:

> A patent may not be obtained though the invention is not identically disclosed or described as set form in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

135. To establish obviousness, it is necessary to prove by clear and convincing evidence that the differences between the claimed invention and the prior art are such that the invention as a whole would have been obvious to one of ordinary skill in the art at the time of the invention. *See Atlas Powder Co. v. E.I du Pont De Nemours & Co.*, 750 F.2d 1569, 1574 (Fed. Cir. 1984). This analysis must be done separately for each claim.

136. Before reaching the ultimate determination of obviousness or non-obviousness, the Court must make findings on:

> (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, (3) the level of ordinary skill in the art, and (4) objective evidence of non-obviousness, such as commercial success, long-felt but unsolved need, failure of others, copying, and unexpected results.

Greenwood v. Hattori Seiko Co., Ltd., 900 F.2d 238, 241 (Fed. Cir. 1990).

137. The analysis under 35 U.S.C. § 103 "requires the oft-difficult but critical step of casting the mind back to the time of the invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Dembiczak,* 175 F.3d 994, 999 (Fed. Cir. 1999). Moreover, finding the elements of the patented invention in the prior art is simply the beginning of the analysis, The Federal Circuit cautions:

> As this court has stated, "virtually all [inventions] are combinations of old elements." Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat (he patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability."

In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998) (quoting *Environmental Designs, Ltd.* v. *Union Oil Co.,* 713 F.2d 693, 698 (Fed. Cir. 1983) and *Sensonics, Inc.* v. *Aerosonic Corp.,* 81 F.3d 1566, 1570 (Fed. Cir. 1996)) (alteration in original)(citations omitted).

138. To prove obviousness, therefore, it is insufficient to demonstrate that the separate elements of the invention existed in the prior art. Rather, there must be some teaching or suggestion in the prior art to combine those elements, *seeArkie Lures, Inc. v. Gene Larew Tackle, Inc.,* 119 F.3d 953, 957 (Fed. Cir. 1997). "[A] showing of a suggestion, teaching, or motivation to combine the prior art references is an "essential evidentiary component of an obviousness holding."" *Brown & Williamson Tobacco Corp.* v. *Philip Morris*

Inc., *229* F.3d 1120, 1124-25 (Fed. Cir. 2000) (quoting *C.R. Bard, Inc.* v. *MS Systems Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998)). "[T]here must be some suggestion, motivation, or teaching in the prior art that would have led a person of ordinary skill in the art to select the references and combine them in a way that would produce the claimed invention." *Karsten Manufacturing Corp.* v. *Cleveland Golf Corp.*, 242 F.3d 1376, 1385 (Fed. Cir. 2001). The showing of a suggestion, teaching or motivation to combine references "must be clear and particular." *In re Dembiczak*, 175 F.3d at 999.

139. Defendants' burden of establishing obviousness in this case is particularly high because all of the prior art references asserted by Defendants at trial were before the examiner. *See Bausch & Lomb, Inc.* v. *Barnes-Hind/Hydrocurve, Inc.*, *796* F.2d 443,447 (Fed. Cir. 1986) ("[W]hen the prior art before the court is the same as mat before the PTO, the burden on the party asserting invalidity is more difficult to meet.").

140. "There is no suggestion to combine ... if a reference *teaches away* from its combination with another source. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant"" *Tec Air, Inc.* v. *Denso Manufacturing Michigan Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999)(emphasis added)(citation omitted) (quoting *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)).

141. Because there was no evidence introduced of any motivation to combine any of the cited prior art references and because each of the references relied upon by Defendants teaches away from the use of Octoxynol 40 in an ophthalmic formulation, Defendants have failed to meet their burden of proof on the obviousness issue. Accordingly, the Court finds, based on these facts, that none of the inventions of the '493 patent would have been obvious to a person of ordinary skill in the art.

142. Furthermore, because there was no evidence introduced that the more detailed inventions of the dependent claims of the '493 patent would have been obvious to a person of ordinary skill in the art at the time of their invention, the Court finds that those dependent claims (Claims 2-7,9-14, and 16) would not have been obvious to such a person.

143. Defendants improperly argue that the only "difference" between the inventions of the '493 patent and the prior art" Octoxyaol 40" would have been suggested by prior art references disclosing other surfactants such the polysorbate 80 "disclosed" in the '151 patent. This focus on the "difference" between the patented invention and the prior art would result in the improper use of hindsight in determining whether the claimed invention is obvious in light of prior art:

> What we stressed in *Kimberly-Clark,* and have repeated many times since, was that 35 U.S.C. § 103 requires analysis of a claimed invention *as a whole:*
>
> > It is true that [the claimed invention] consists of a

> combination of old elements so arranged as to perform certain related functions. It is immaterial to the issue, however, that all of the elements were old in other contexts. *What must be found obvious to defeat the patent is the claimed combination.*
>
> Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness.

Gillette Co. v. *S.C, Johnson & Son, Inc.*, 919 F.2d 720,724-25 (Fed. Cir. 1990) (quoting *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437,1448 (Fed. Crr. 1984)) (emphasis and alteration in original) (citation omitted). Defendants' focus on Octoxynol 40 as an obvious "substitution" for, *e.g.*, polysorbate 80 violates this fundamental tenet of the obviousness analysis.

144. "What is "[c]ritical to the analysis is an understanding *of the particular results* achieved by the new combination." *Id. (quoting Interconnect Planning Corp. v. Feil,* 114 F.2d 1132, 1143 (Fed. Cir. 1985)) (emphasis added). As the Federal Circuit held in *Gillette* with respect to a chemical composition for a shaving gel:

> There is no question that each component of [the patented] composition was separately known in the prior art.

> What was not known or suggested, however, was the composition that resulted from the combination of those components, and its unique properties. As [the patent-owner] succinctly states,
>
> > The... invention is a post-foaming gel composed of four components, all of which interact to provide a particular kind of gel with suitable shaving characteristics" in fact, shaving properties superior to any other product on the market The invention as a whole is that composition, with its gel form, and its properties.

Id. Similarly, here, Plaintiffs' inventions are unique ophthalmic compositions, their preservative systems, and their methods of use. The results of Plaintiffs' inventions are drug formulations that remain stable and antimicrobially effective over their reasonable shelf life.

145. Furthermore, Plaintiffs introduced objective evidence that strongly attests to the non-obviousness of the inventions of the '493 patent. In this regard, the Court has considered the objective evidence of non-obviousness, such as, for example, commercial success and industry acclaim, licensing and royalty payments, unsuccessful attempts to create the invention, long-felt need, and unexpected results. *See Apple Computer, Inc. v. Articulate Systems, Inc.*, 234 F.3d 14, 26 (Fed. Cir. 2000); *Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 1376-80 (Fed. Cir. 2000); *John Charles Designs, Inc. v.*

Queen International Design, Inc., 940 F. Supp. 1516, 1521 (C.D. Cal. 1996). As the Federal Circuit has noted, "evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decision maker remains in doubt after reviewing the art." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-39 (Fed. Cir. 1983). In many cases, such as in this case, the objective evidence of non-obviousness, which must be considered by the Court, includes facts that arise after the issuance of the patent and that therefore could not have been considered by the patent examiner.

146. The commercial success of ACULAR®, a drug that embodies and practices the inventions of the '493 patent, supports the Court's rejection of Defendants' argument that the claims of the '493 patent are obvious. Obviously, the examiner of the '493 patent application could not have considered this objective evidence of commercial success because these sales of ACULAR® occurred after patent issuance.

147. A nexus between the patented inventions and commercial success is presumed to exist when the features of the patented drug are embodied in a commercially marketed product. As the Federal Circuit held in *Brown & Williamson Tobacco Corp.* v. *Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000), "[a] nexus between commercial success and the claimed features is required. *However, if the marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed and the burden shifts*

to the party asserting obviousness to present evidence to rebut the presumed nexus." (emphasis added, citations omitted).

148. There is no dispute that ACULAR® or the use of ACULAR® to treat ophthalmic disease embodies the subject matter of each claim of the '493 patent. There is no dispute that ACULAR® is co-extensive with Claim 7 of the '493 patent, which claims ACULAR®'s ingredients exactly. There is no dispute mat using ACULAR® to treat ophthalmic disease is co extensive with Claim 14 of the '493 patent, which claims a method of treating ophthalmic disease by using the formulation of Claim 7. Thus, a nexus between ACULAR®'s commercial success and the claims of the '493 patent is presumed, and the burden rests on Defendants to disprove the existence of the nexus. *See id.*

149. Defendants have not disproved a nexus between ACULAR®'s commercial success and the formulations and treatment methods claimed in the '493 patent. The experiences of Voltaren and Acular PF® demonstrate that ACULAR®'s commercial success derives from its patented features because neither Voltaren nor Acular PF® contain the patented combination of an NSAID, a quaternary ammonium preservative, and Octoxynol 40. Moreover, the fact that ACULAR® has perfoimed far better than Acular PF® demonstrates that the multi-dose aspect of ACULAR® has been a contributor to ACULAR®'s

commercial success. ACULAR® is the only drug that contains an NSAID, a quaternary ammonium preservative, and Octoxynol 40, and no other ophthalmic anti-inflammatory has achieved the kind of commercial success seen by ACULAR®.

150. The non-obviousness of the '493 patent is further demonstrated by the fact that a third party (Allergan) entered into an exclusive distribution agreement with Syntex before the '493 patent was issued and has paid Syntex over $133 million in royalties under that agreement. *See Arkie Lures,* 119 F.3d at 957 (noting that licensing activity "may be highly probative of the issue of nonobviousness"). As with the evidence of commercial success, this "highly probative" evidence of royalty payments could not have been considered by the patent examiner because it had not yet occurred.

151. Copying of the patented drug by Defendants is also objective evidence of the non-obviousness of the claims of the '493 patent. *See Apple Computer,* 234 F.3d at 26. This objective evidence of copying could not have been considered by the examiner.

152. The fact that the inventions satisfied a long-felt need present at Syntex for a . ketorolac-based ophthalmic drug also weighs strongly in favor of a finding of non-obviousness. *See Hewlett-Packard Co.* v. *Tel-Design, Inc.,* 460 F.2d 625, 631 (9th Cir. 1972) ("The evidence of prior unsuccessful attempts to solve the same problem established both the pressing need for such a solution as well as the fact that the solution had not been obvious to those whom the court found to

be highly skilled in the pertinent art."). As stated by the Federal Circuit in a similar case:

> Pratt's extensive efforts to solve the problem of isolating the weighing system indicate the absence of a suggestion to combine the Brewster machine with the positive intermixing elements of the volume machines. These efforts by Pratt tend to show that one skilled in the art would have had no reasonable expectation of success in combining the prior art machines in question. Long-felt need in the face of prior art later asserted to lead to a solution tends to negate the proposition that the combination of such prior art would have been obvious.

Micro Chemical Inc. v. *Great Plains Chemical Co., Inc.*, 103 F.3d 1538, 1547 (Fed. Cir. 1997) (citations omitted). The fact that Syntex scientists tried unsuccessfully for several years to formulate a ketorolac tromethamine ophthalmic solution strongly suggests that the inventions of the patent were not obvious.

153. Finally, a showing mat the claimed inventions achieved "unexpected results" is objective evidence of the non-obviousness of the claims of the '493 patent. *See Apple Computer,* 234 F.3d at 26. The inventions of the '493 patent produced unexpected results in that a largely unknown surfactant that had not been used in any ophthalmic drug prior to ACULAR®, Octoxynol 40, helped the claimed

formulations to achieve the desired stability better than some of the other known surfactants at the time, such as Myri 52 and Tween 80, and better than the closest prior art cited by the examiner, Octoxynol 5. Ms. Lidgate's test results showing that not all surfactants had the same positive effect in a ketorolac tromethamine/BAC formulation as did Octoxynol 40 represent objective evidence of the non-obviousness of the '493 patent claims.

154. In response to this showing of unexpected results, Defendants contend that they have also compared Octoxynol 40 to other surfactants and that their test results differ from those of Ms. Lidgate. Therefore, Defendants argue, the claims of the *493 patent are invalid as obvious because the evidence of unexpected results presented by Syntex during the prosecution of the *493 patent has been contradicted. Defendants' argument, however, demonstrates a fundamental misconception regarding the place of evidence of unexpected results in the law of obviousness. Evidence ofunexpected results is oneof several objective indicia of non-obviousness. *SeeApple Computer,* 234 F.3d at 26; *Brown & Williamson,* 229 F.3d at 1129.

155. Contrary to Defendants' argument, however, there is no requirement that a claimed invention attain an unexpected result before a conclusion of non-obviousness may be reached. *See Panduit Corp. v. Dennison Manufacturing Co., 11A* F.2d 1082,1098 (Fed. Cir. 1985), *vacated on other grounds by Dennison Manufacturing Co.* v. *Panduit Corp.*, *415* U.S. 809 (1986) (per curiam). As with the other objective indicia, the absence ofunexpected

results is no more than a "neutral factor" in the determination of patentability and is not dispositive on the question of obviousness.

156. The non-obviousness of the '493 patent claims is demonstrated by (1) the fact that Octoxynol 40 was never used in a drug before the inventions of the '493 patent; (2) the fact that the prior art does not suggest the combinations of the claimed inventions and in fact suggests the use of other surfactants or no surfactant at all; and (3) the strong and largely undisputed objective evidence of ACULAR®'s commercial success, the exclusive distribution agreement between Syntex and Allergan, the copying of ACULAR® by Defendants, Syntex's lengthy efforts to invent a ketorolac tromemamine formulation, and unexpected results.

157. As established by the findings of fact set forth in paragraphs 112 through 133, Defendants have failed to prove by clear and convincing evidence that any claim of the '493 patent is invalid due to obviousness.

VII. INEQUITABLE CONDUCT
FINDINGS OF FACT

158. The '493 patent issued on May 5,1992, based on Application No. 07/624,027, which was filed on December 7, 1990. This application was a continuation of application no. 07/096,173, filed on September 11, 1987. The '493 patent named Dr. Fu and Ms. Lidgate as joint inventors and Syntex as the assignee. The attorney who prosecuted the continuation application that resulted in the '493

patent was Derek Freyberg, in-house counsel for Syntex. There was no evidence introduced that anyone other than Dr. Fu, Ms. Lidgate, and Dr. Freyberg was substantively involved in the preparation or prosecution of the application that led to the '493 patent.

159. An Information Disclosure Statement ("IDS") was filed with each application. The examiner's initials appear in the IDS beside each document that is cited in the IDS. Therefore, the examiner considered each document cited in the IDS. Trial Exs. 024, 035; R.T. 759:17-760:14.

160. The results of Ms. Lidgate's study of formulations containing ketorolac tromethamine, BAC, and three different surfactants - Octoxynol 40, Tween 80, and Myrj 52 - were disclosed to the Examiner during the examination of the parent Application No. 07/096,173. These results showed that solutions containing Octoxynol 40 remained clear under a variety of storage conditions while solutions containing Tween 80 and Myrj 52 became turbid. During the prosecution of the application that became the '493 patent, Application No. 07/624,027, Dr. Freyberg referred the Examiner back to these results. This disclosure of test results to the PTO accurately described the tests performed and the results observed by Ms. Lidgate. There was no evidence introduced that the disclosure contained any false or misleading statement or that any fact material to the patentability of the application was withheld from the Examiner with an intent to deceive the Examiner. Trial Exs. 204,205, 009, 024 at SYN0000280, 035 at SYN0000062; R.T. 695:1-701:14, 761:2-762:9.

161. On March 5,1991, the PTO issued a rejection of all of the claims of Application No. 07/624,027 as obvious over the prior art. The Examiner noted that the Gilbert and Han patents both taught the use of "nonionic surfactants" as stabilizing agents and stated that "[t]he mere substitution of one nonionic for another, that is, the nonionic of McCutcheon's for the nonionic of the primary reference is not deemed a patentable distinction in the absence of a showing of some unobvious result." Specifically with respect to pending claims 37 and 38, the claims were rejected as obvious over the Nadir and Schmolka references. The Nadir reference suggested the use of Octoxynol 5 in conjunction with antibacterial preservatives. Trial Ex. 035 at SYN0000045-49, SYN0000090; R.T. 766:3-768:22, 771:1-11.

162. In response to the March 5,1991 rejection, Dr. Freyberg submitted, on September 5,1991, an Amendment of the claims. Specifically in response to the Examiner's rejection of claims 37 and 38 over the Nadir reference, Dr. Freyberg submitted a declaration of Ms. Lidgate (the "Lidgate Declaration"). The Lidgate Declaration included the results of a test performed by Ms. Lidgate that compared formulations containing Octoxynol 40, Octoxynol 5, and Octoxynol 3. Trial Ex. 035 at SYN0000057-64; R.T. 769:11-770:25.

163. The September 5,1991 Amendment stated as follows:

> Applicants have shown in the prosecution of the parent to this application that other nonionic

> surfactants, such as Tween and Myrj, fail to act as stabilizers in the claimed formulations; and the enclosed Declaration of Deborah M. Lidgate demonstrates that certain octoxynols are unsatisfactory.

Thus, the Amendment attempted to convince the Examiner that he was wrong in treating all nonionic surfactants alike because at least some surfactants, including certain octoxynols, would not work to stabilize the claimed formulations. Trial Ex. 035 at SYN0000062.

164. When Ms. Lidgate turned her data from the experiment in question over to Syntex's patent department, the data included the results of experiments on formulations containing Octoxynol 40, Octoxynol 5, Octoxynol 3, and Octoxynol 12.5. Included in those results was Ms. Lidgate's observation that, after three months of stability testing, the formulations containing Octoxynol 40 and Octoxynol 12.5 looked equivalent R.T. 658:1-660:23.

165. Although Ms. Lidgate noted that the formulations containing Octoxynol 40 and Octoxynol 12.5 looked equivalent, she did not conclude that they were equivalent in any other respect In particular, Ms, Lidgate had no evidence that the formulation containing Octoxynol 12.5 would pass the "USP challenge" test for antibacterial effectiveness. R.T. 651:13-652:12, 660:16-661:8.

166. While Ms. Lidgate did not make the decision as to which of the octoxynols would be

included in the Lidgate Declaration, she believed the Declaration to be accurate and truthful at the time that she signed it. Ms. Lidgate testified that she had no reservations about the fact that the Declaration did not mention Octoxynol 12.5 because the purpose of the Declaration was to show that not all octoxynols would be suitable for use in the patented formulations. R.T. 661:9- 662:6.

167. Dr. Freyberg did not include any reference to Octoxynol 12.5 hi the Lidgate Declaration because the purpose of the Declaration was to compare the invention with the prior art cited by the examkter"that is, Octoxynol 5. The examiner cited no prior art reference that described an ophthalmic formulation using Octoxynol 12.5, and there is no evidence in the record of the existence of any such prior art reference. R.T. 772:5-774:13.

168. Based on the evidence presented, the Court finds that the Lidgate Declaration was not rendered misleading by the fact that it did not include Ms. Lidgate's results with respect to the formulation containing Octoxynol 12.5. Given the basis for the examiner's rejection, the Court finds that Declaration sought to address the concern that not all octoxynols acted alike and, specifically, that the Octoxynol 5 mentioned in Nadir behaved very differently from Octoxynol 40. In addition, the Court finds that the purpose of the Declaration was *not* to show that Octoxynol 40 was the *only* Octoxynol that would result in a visually clear formulation; indeed, the specification of the '493 patent itself mentions the use of another Octoxynol, Octoxynol 10. '493 patent, col. 4, lines 32-41, Furthermore, the Lidgate Declaration

refers to Octoxynol 40 as being suitable for use in an ophthalmic formulation and Octoxynols 5 and 3 as being unsuitable.

169. Having considered the record in its entirety, including the five year course of prosecution of the '493 patent and the scope and results of Plaintiffs testing over that time, the Court finds that Ms. Lidgate had no evidence that Octoxynol 12.5 would perform in equivalent fashion or outperform the results achieved through use of the formulation containing Octoxynol 40. For example, Ms. Lidgate could not account for whether Octoxynol 12.5 in the formulation at issue would pass the "USP challenge" test for antibacterial effectiveness. Therefore, Ms. Lidgate had no factual basis for drawing any conclusion regarding the suitability or unsuitability of Octoxynol 12.5 in an ophthalmic formulation. Defendants arguments based upon the existence of the Schmoka reference does not alter the Court's conclusion in this regard. R.T. 651:13-652:12, 660:16-662:6.

170. Ms. Lidgate's experiments that led to the submission of the Lidgate Declaration made use of a "control" "that is, a formulation to which other formulations are compared. The formulation containing Octoxynol 40 was the formulation that other formulations were being compared against, and it therefore acted as the "control" formulation in the experiments. R.T. 621:6-622:17.

171. There was no evidence introduced that Dr. Fu, Ms. Lidgate, or Dr. Freyberg were ever aware of any particular test results obtained by De Mei Leung

in connection with the ketorolac tromethamine ophthalmic project. Therefore, these test results have no bearing on the inequitable conduct issue in this case. Trial Ex. ML.

172. Having observed the testimony of Dr. Freyberg and Ms. Lidgate, and evaluated their testimony in light of the evidentiary record in this matter, the Court finds the testimony of Ms. Lidgate and Dr. Freyberg credible. As such, the Court finds that there was no intent on the part of Dr. Fu, Ms. Lidgate, or Dr. Freyberg to mislead the PTO in connection with the prosecution of the '493 patent

173. Defendants have not proved by clear and convincing evidence that Dr. Fu, Ms. Lidgate, or Dr. Freyberg violated a duty of good faith and candor or violated a duty of disclosure owed to the Patent and Trademark: Office in connection with the application for or prosecution of the "493 patent.

174. Defendants have not proved by clear and convincing evidence that any person associated with Syntex who was substantively involved in the preparation or prosecution of the application for the '493 patent violated a duty of good faith and candor or violated a duty of disclosure owed to the Patent and Trademark Office in connection with the application for or prosecution of the '493 patent.

CONCLUSIONS OF LAW

175. The defense of inequitable conduct in response to a patent infringement suit is strongly disfavored and is successful only in extremely rare

circumstances. As the Federal Circuit has noted, ""[inequitable conduct" is not, or should not be, a magic incantation to be asserted against every patentee." *FMC Corp.* v. *Manitowoc Co., Inc.*, 835 F.2d 1411, 1415 (Fed. Cir. 1987).

176. The Federal Circuit has imposed a heavy burden on the party alleging inequitable conduct:

> [O]ne alleging "failure to disclose" type inequitable conduct must prove with sufficient clarity that: (1) information exists that is material; (2) the applicant or his or her attorney knew of this information and that it was material; and (3) the applicant or his or her attorney failed to disclose the information with the intent to mislead the PTO.

Brasseler, U.S.A. I, L.P. v. Stryker Sales Corp., 267 F.3d 1370, 1375 (Fed. Cir. 2001). Moreover, the required intent to mislead the PTO must be in the form of true decepuWit cannot be inferred from mere negligence or even gross negligence on the part of the applicant who fails to disclose material information. *See Kingsdown Medical Consultants, Ltd.* v. *Hollister Inc*, 863 F.2d 867, 876 (Fed. Cir. 1988).[9]

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[9] The standard for what is considered ^material" for inequitable conduct purposes changed on March 16,1992. Prior to that date, information was considered "material" when there was "a substantial likelihood that a reasonable examiner would consider it important,"" whereas after that date, ^material" information was information that was not cumulative and that either (1) established, "by itself or in combination with other information, a prima facie case of unpatentability of a claim" or (2) refuted or was inconsistent with a position taken by the applicant

177. Only if the requisite levels of materiality and. intent are shown must a court then determine whether the equities warrant a conclusion that the patentee has engaged in inequitable conduct *See id.* at 1178. However, the patentee has no burden to produce evidence of good faith, and a court is not required to balance materiality and intent when no threshold finding of intent to mislead is made. *See Nordberg, Inc.* v. *Telsmith, Inc.*, 82 F.3d 394, 398 (Fed. Cir. 1996).

178. Defendants argue that "Syntex" committed inequitable conduct by failing to disclose certain information to the Patent and Trademark Office. The Federal Circuit, however, has defined the categories of persons to whom the duty of candor and good faith applies as follows:

> Under PTO rules, the duty to disclose information material to patentability rests on the inventor, on each attorney or agent who prepares or prosecutes an application and on every other *individual* who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee, or with anyone to whom there is an obligation to assign the application.

Molins, 48 F.3d at 1178 n.6 (emphasis added) (citing 37 C.F.R. § 1.56); *see also Brasseler*, 267 F.3d at 1383 n.6 ("*Individuals* associated with the riling or prosecution of an application have a duty to disclose material

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See Molins PLC v. *Textron, Inc.*, 48 R3d 1172,1179 n.8 (Fed. Cir. 1995).

information commensurate with their involvement") (emphasis added).

179. Moreover, the Federal Circuit has held that the duty of disclosure extends only to the "relevant" employees of a corporation" that is, the inventors and patent counsel. *See Nordberg,* 82 F.3d at 396-97. Therefore, a patent cannot be held unenforceable for inequitable conduct based on information that was contained in a corporation's files but was not known to those employees under a duty to disclose. *See id.*

180. MPEP §2001.01 further clarifies that "[t]he duty applies only to individuals, not to organizations. For instance, the duty of disclosure *would not apply to a corporation or institution as such.* However, it would apply to individuals within the corporation or institution who were substantively involved in the preparation or prosecution of the application, and actions by such individuals may affect the rights of the corporation or institution." (Emphasis added).

181. Despite the plain language of the case law and the MPEP, Defendants cite *Critikon, Inc.* v. *Becton Dickinson Vascular Access, Inc.,* 120 F.3d 1253 (Fed Cir. 1997), for the proposition that the duty of candor applied to Syntex as a corporation rather than just to the individuals involved in the prosecution of the '493 patent. In *Critikon,* however, the court found that the prosecuting patent attorneys-were intimately familiar with the information withheld from the PTO:

> Both of Critikon's patent counsel who were involved in the prosecution of the Lemieux patents, Mr. Colletti and Mr. York, had reviewed the [withheld] McDonald patent in detail.
>
> . . . .
>
> [T]he patent counsel who were handling the reissue proceedings were keenly aware of the litigation and the issues involved prior to the resolution of the reissue proceedings. However, there is no evidence in the record that anyone reported the ongoing litigation to the PTO. Nor is there any evidence as to a good faith explanation as to why it was never reported.

Id. at 1256-57. Nowhere does *Critikon* suggest that a corporation has a duty of candor to the PTO *separate* from the duty owed by the individual applicants and prosecutors involved in the prosecution of a particular patent or that a corporation is required to disclose information not known to those applicants and prosecutors.

182. Defendants' argument that the submission of the Lidgate Declaration amounted to inequitable conduct fails because that Declaration was not misleading in any fashion and did not fail to disclose material information to the PTO. As noted above, the Lidgate Declaration did not purport to show that Octoxynol 40 worked better than every other nonionic surfactant, but only that all nonionic surfactants, and particularly all octoxynols, did not act alike. The Declaration accurately stated that

Octoxynol 40 was suitable for use in ophthalmic formulations, whereas Octoxynol 5 and Octoxynol 3 were not.

183. An affidavit offering comparison test data need only present "a fair and accurate demonstration of the closest prior art of which the applicant [was] aware" at the time of the application. *See Avco Corp. v. PPG Industries, Inc.*, 867 F. Supp. 84, 92 (D. Mass. 1994). Because the Examiner had rejected certain claims of the pending application based on Nadir, which discussed the use of Octoxynol 5, the Lidgate Declaration properly compared the claimed formulation, containing Octoxynol 40, to the closest art cited by the examiner. There was no evidence introduced of any prior art reference mentioning Octoxynol 12.5. Defendants arguments regarding Plaintiffs failure to disclose anew the existence of Polysorbate 80 does not compel a different conclusion where, as here, the Examiner was already aware of its existence as a result of the prosecution history related to the 493 patent.

184. Defendants have not proved that Dr. Fu, Ms. Lidgate, or Dr. Freyberg intended to mislead the PTO. As the Federal Circuit has recognized, "[s]imple negligence, oversight, or an erroneous judgment made in good faith is insufficient to establish intent" to mislead during the prosecution of a patent *Specialty Composites* v. *Cabot Corp.*, 845 F.2d 981, 992 (Fed. Cir. 1988). Therefore, mere nondisclosure of test results cannot be a predicate for a finding of inequitable conduct in the absence of clear and convincing evidence of an intent to defraud the PTO. *See, e.g., Avco,* 867 F. Supp. at 94 (finding that patent

applicant's *intentional failure* to disclose to the PTO certain material comparison tests between product that was subject of application and competitor's product was not inequitable conduct absent clear and convincing proof that applicant intended affirmatively to mislead the PTO); *Hoecftst Celanese Corp.* v. *BP Chemicals Ltd.*, 846 F. Supp. 542, 548 (S*D.* Tex. 1994) (holding that even if the comparative test data presented to the PTO could have been more complete, the evidence was devoid of proof of an intent to deceive). There was no evidence introduced, direct or circumstantial, of any intent to deceive the PTO.[10]

185. As established by the findings of fact set forth in paragraphs 158 through 174, Defendants have failed to prove by clear and convincing evidence that any claim of the '493 patent is unenforceable due to inequitable conduct

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[10] The Federal Circuit's pronouncements in *Bristol-Myers Squibb Co.* v. *Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226 (Fed. Cir. 2003), do not impact this conclusion. *Bristol-Myers* held that "where withheld information *is material and the patentee knew or should have know[n] of that materiality,* he or she can expect to have great difficulty in establishing subjective good faith *sufficient to overcome an inference of intent to mislead." Id.* at 1239 (emphasis added). In this case, as discussed above, mere is no evidence that the inventors or the patent attorney withheld any material information, let alone that they knew or should have known of its materiality, nor is there any evidence from which intent to mislead could be inferred.

VIII. REMEDIES AND EXCEPTIONAL CASE UNDER 35 U.S.C. § 285

Findings of Fact

186. The Court incorporates its findings of feet and conclusions of law on the issues of infringement, validity and enforceability, as set forth above.

187. Defendants, in response to Plaintiff's Second Set of Request for Production of Documents, indicated that they were no relying upon any opinion of counsel as a defense to Plaintiff's allegation that this is an exceptional case under 35 U.S.C. Section 285. In addition, in response to Plaintiffs Second Set of Interrogatories, Defendants indicated that they were not relying upon advice of Counsel as a Defense to Plaintiffs allegation that this is an exceptional case. R.T. 1772:7-1773:16.

188. Defendants were aware of the '493 patent at the time that they decided to copy ACULAR®. Trial Ex. 299 at 31:18-32:15, 32:21-33:9.

189. Prior to the submission of ANDA 76-109, Defendants' had not performed a preservative effectiveness test on any ketorolac tromethamine ophthalmic solution that had been prepared at least a year before the test. Trial Ex. 302; R-T. 1774:12-25.

190. Dr. Sherman was of the opinion, based upon his knowledge and experience in the pharmaceutical field, that the 493 patent was invalid because he believed that 040 was not unique in its

alleged ability to stabilize the claimed formulation. Trial Ex. IG, N2353; IJ- Sherman Depo: 18:17-23; 42:22-43:8; 89:14; 36:16-20; 47:3-11.

191. In submitting ANDA 76-109, Defendants took the position that the '493 patent was invalid "because it was obvious in light of prior art and that Syntex had engaged in Inequitable Conduct in securing the patent. Trial Exh. E.

192. Dr. Sherman's initial belief was supported by Novex' pre-litigation testing of samples involving ACULAR formulations with a surfactant other than 040. Exh. LJ: Van Doomik Depo: 22:21-24; JF, N2316-2318. Prior to the lawsuit, Mr. Van Doomik reported the results of the "first batch" of samples reflecting the results of Acular formulations with a surfactant other than 040. Trial Exhs. GF, N2321; LF N2324; HG-N2354; IG-N2353.

193. After several months, the first batch of samples remained clear. Therefore, Dr. Sherman opined that 040 was not necessary in the formulations claimed by the '493 patent, and determined that the first batch would pass the USP, antimicrobial test because passing the USP test is dependant on the presence of a preservative (e.g. BAC) and not the use of a surfactant. Trial Exh. MF-N2327; IF:Sherman Depo: 60:2-11; 100:19-101-11; Dr. Sherman also instituted a "second batch" of testing related to KT/BAC samples, to determine the clarity of these samples over 12 months and 20 months. Trial Exh. IJ: Sherman Depo: 108-109:5.

194. Based upon these tests and others, Dr. Sherman held a good faith belief that the Novex formulation did not infringe the claims of the '493 patent.

195. While the Court' concerns regarding Defendants' inability to duplicate the ingredients used by Plaintiffs in the prosecution of the '493 patent, including the homolog content of the BAC used in the "batches" subjected to testing, resulted in this Court according less weight to these tests, these results nevertheless provide evidentiary support for Dr. Sherman's belief regarding the validity of the '493 patent.

196. In addition, Defendants' trial evidence raised significant, but ultimately unsuccessful concerns, regarding the enforceability of the '493 patent in light of asserted inequitable conduct before the PTO.

197. Based upon the testing regime instituted by Dr. Sherman, the Court finds that defendants' had a reasonable basis for concluding that the claims of the '493 patent were invalid as more fully setforth above. Moreover, the Court finds Defendants had a reasonable and good faith basis for concluding, both prior to and during the trial of this matter, that the '493 patent was unenforceable as a result of Inequitable Conduct in the prosecution of the '493 patent given that the resolution of this defense was intensely factual and turned on credibility findings made by the Court with respect to the testimony of the witnesses.

198. As such, based on the totality of the evidentiary record in this matter, the Court finds that Plaintiffs have failed to establish that Defendants willfully infringed the claims asserted in the '493 patent However, even were the Court to assume that Defendants' did engage in willful infringement, the Court finds, based upon the totality of the evidentiary record in this matter that this case is not an exceptional case within the meaning of 35 U.S.C. Section 285 and 35 U.S.C. Section 271(e)4.

CONCLUSIONS OF LAW

199. 35 U.S.C. § 271(e)(4) provides, in relevant part, that for an act of infringement under 35 U.S.C. § 271(e)(2),

> (A) the court shall order the effective date of any approval of the drug... involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed, [and]
> (B) injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug

Because this Court has found that the Mag of Defendants' ANDA infringed each claim of the '493 patent, and because Defendants have not proved that any of those sixteen infringed claims is invalid or unenforceable, the Court orders as follows: (1) that the

effective date of any approval of Defendants' ANDA under § 505(j) of the Federal Food, Drug & Cosmetic Act (21 U.S.C. § 355(j)) for the drug product "Ketorolac Tromethamine Ophthalmic Solution 0.5%" be a date not earlier than the expiration date of the '493 patent; (2) that Defendants, and all persons and entities acting in concert with Defendants, be enjoined from making, using, selling, or offering for sale in the United States, or importing into the United States, any products that infringe, induce the infringement of, or contributorily infringe the '493 patent; and (3) that Defendants, and all persons and entities acting in concert with Defendants, be enjoined from making preparations to make, use, sell, or offer for sale Ketorolac Tromemamine Ophthaknic Solution 0.5% in the United States.

200. The court in exceptional cases may award reasonable attorney fees to the prevailing party. 35 U.S.C. Section 285. 35 U.S.C. § 271(e)(4) also specifically authorizes this additional remedy. A party seeking attorney's fees must prove the "exceptional" nature of the case by clear and convincing evidence. *Eltech Sys. Corp, v. PPG Indus., Inc.*, 903 F.2d 805, 810011 (Fed.Cir.1990). The Federal Circuit has recognized many varieties of misconduct that make a case exceptional for a fee award, including but not limited to: willful infringement, inequitable conduct before the PTO, offensive litigation tactics, vexatious or unjustified litigation, or frivolous filings. *Yamanouchi Pharmaceutical* v. *Danbury Pharmacal,* 231 F.3d 1339, 1347 (Fed.Cir.2000).

201. "[T]he joint operation of"" 271(e) and 285 require the [35 U.S.C. § 271(e)(2)] infringer to display

care and regard for the strict standards of the Hatch-Waxman Act when challenging patent validity.... Specifically, a paragraph IV filing requires "a certification, in the opinion of the applicant *and to the best of his knowledge,* [that] each patent... for which the applicant is seeking approval... is invalid." *Yamanouchi Pharmaceutical Co., Ltd.* v. *Danbury Pharmacal, Inc.,* 231 F.3d 1339,1347 (Fed. Cir. 2000) (emphasis and alterations in original). "The Hatch-Waxman Act thus imposes a duty of care on an ANDA certifier." *Id.* (affirming award of attorneys fees on the ground that the defendant's ANDA certification of patent invalidity and its invalidity case at trial contained "glaring weaknesses").

202. Whether infringement is willful is a question of fact, and must be established by clear and convincing evidence." *Comark Communications v. Harris Corp.,* 156 F.3d 1182, 1190 (Fed. Cir. 1998). The issue of willfulness is analyzed under the "totality of circumstances" and the primary consideration is whether the infringer, acting upon good faith and upon due inquiry, has sound reason to believe that it had the right to act in the manner that was found to be infringing" SRI Int'l v. *Advanced Tech. Lab. Inc.,* 127 F.3d 1462, 1464-65 (Fed. Cir. 1997).

203. Factors that may be considered in determining willfulness include whether the infringer deliberately copied, whether the infringer investigated the scope of the patent and had formed a good faith belief that the patent was invalid or not infringed, and the infringer's behavior as a party to the litigation. *Boat* v. *Four Star Corp.,* 807 F.2d 1567,1572 (Fed.Cir. 1986) overruled on other grounds by AC. *Ackerman*

Co. v, if. *L. Chaises Const.* Co., 960 F.2d 1020 (Fed. Cir. 1992); an infringer "may generally avoid enhanced damages with a meritorious good faith defense and a substantial challenge to infringement" *Delta-Xv. Baker Hughes Production Tools,* 984 F.2d 410, 413-14 (Fed. Cir. 1993); *Elector Medical Systems, S.A.* v. *Cooper lif eSciences, Inc.,* 34 F.3d 1048 (Fed. Cir. 1994); *Laitram Corp.* v. *NEC Corp.,* 115 F.3d 947, 955 (Fed. Cir. 1997).

204. The filing of an ANDA, by its very nature is a "highly artificial act of infringement," therefore a court need not elevate the ANDA certification into a finding of willful infringement. Yamanouchi Pharmaceutical v. Danbury Pharmacal, 231 F.3d 1339, 1347 (Fed. Cir. 2000).

205. The totality of evidence presented at trial shows that Defendants' did not willfully infringe the '493 patent.

206. Dr. Sherman had a reasonable basis for concluding that the claims of the '493 patent were invalid as more fully set forth above. Moreover, the Court finds Defendants had a reasonable and good faith basis for concluding, both prior to and during the trial of this matter, that the '493 patent was unenforceable as a result of Inequitable Conduct in the prosecution of the '493 patent.

207. Even if this Court determined, on this record, that Defendants willfully infringed the '493 patent, Plaintiffs are not entitled to attorneys' fees because the Court finds, on this record including Defendants' ANDA certification, its pre-filing testing

and the evidence produced at trial that Plaintiff has not established by clear and convincing evidence that the case is exceptional.

208. Given these findings, neither party is entitled to attorneys' fees under 35 U.S.C. § 285 and 271(e).

IX. CONCLUSION

209. The Court incorporates each of the findings of fact and conclusions of law set forth above as if fully stated here and based thereon finds: that Defendants' have infringed the claims of the '493 patent, and that the claims of the M93 patent are valid and enforceable.

210. Neither plaintiffs nor defendants are entitled to attorneys' fees under 35 U.S.C. § 285 and 271(e).

IT IS SO ORDERED.

Dated: December 29, 2003

/s/ Martin J. Jenkins
Martin J. Jenkins
United States District Judge

United States Patent

Patent Number: 5,110,493

Cherng-Chyi. et al.

Date of Patent: May 5, 1992

OPHTHALMIC NSAID FORMULATIONS CONTAINING A QUATERNARY AMMONIUM PRESERVATIVE AND A NONIONIC SURFACTANT

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Continuation of Ser. No. 96,173, Sep. 11, 1987, abandoned.

Int. Cl.$_5$ A61K 31/40

U.S. Cl. **514/413;** 252/106; 514,912; 514/914

Field of Search 514/413, 912, 914; 252/106

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Abstract

Stable, clear, antimicrobially effective, ophthalmic formulations include an ophthalmologically effective amount of a drug, especially a --COOH group-containing drug or a NSAID, and a preservative system formed of a quaternary ammonium preservative and a nonionic surfactant, all in an aqueous vehicle. These formulations are useful for treating diseases that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy

and conjunctivitis, or any trauma caused by eye surgery or eye injury.

16 Claims, No Drawings

OPHTHALMIC NSAID FORMULATIONS CONTAINING A QUATERNARY AMMONIUM PRESERVATIVE AND A NONIONIC SURFACTANT

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation of our copending application Ser. No. 07/096,173, filed Sep. 11, 1987 now abandoned.

BACKGROUND OF THE INVENTION

The present invention relates to improved ophthalmic formulations, particularly to ophthalmic formulations for anti-inflammatory drugs, and specifically to an improved preservative system for ophthalmic formulations of carboxyl ("--COOH") group-containing drugs, especially non-steroidal anti-inflammatory drugs ("NSAIDs").

The invention also relates to methods of using these formulations for treating diseases that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury.

The topical use of NSAIDs, particularly pyrrolo pyrroles, in the treatment of ophthalmic diseases was first taught in U.S. Pat. No. 4,454,151, where NSAID compounds (such as those described in U.S. Pat. Nos. 4,089,969; 4,232,038; 4,087,539 and 4,097,579) were exemplified in formulation with NaH_2PO_4 H_2O, $Na_2HPO_4H_2O$, NaCl, benzalkonium chloride ("BAC") and sterilized water. While the formulations described in the '151 patent were efficacious, a complex was found to form between the NSAID and the BAC. The formulations did not, therefore, have the stability desired for shelf life in commercial applications. A reasonable minimum shelf life is at least about one year, representing sufficient time to package, ship, and store a formulation without having to replace expired stock too frequently. Thus, the present invention entails an improvement over the formulations described in the '151 patent.

In general, an ophthalmic formulation contains an active compound and various ophthalmologically acceptable excipients, in the form of a solution, an ointment, a suspension, etc. An excipient is ophthalmologically acceptable if it is non-irritating to the eye and if its active ingredient penetrates the blood-aqueous barrier and/or difuses through the various ocular substructures to the site where it is pharmacologically active. The excipients can include a tonicifier, a preservative, a surfactant, a buffering system, a chelating agent, a viscosity agent as well as other stabilizing agents. Ophthalmic formulations must be sterile, and if intended for multiple dosing

regimens, must be preserved with an effective anti-microbial agent.

Organo-mercurials (e.g., thimerosal, phenylmercuric acetate and phenylmercuric nitrate) have been used extensively as the preservative in ophthalmic solutions. These compounds, however, pose difficulties due to potential mercury toxicity as well as poor chemical stability. Benzalkonium chloride, a quaternary ammonium compound, has been widely used in ophthalmic solutions, and is considered to be the preservative of choice. However, BAC has typically been considered to be incompatible with anionic drugs (e.g., salicylates or nitrates, etc.) and can be inactivated by surfactants.

Many NSAIDs (such as ketorolac, indomethacin, flurbiprofen and suprofen) are being developed for ocular use because of their activity as anti-inflammatory agents as well as their ability to prevent cystoid macular edema.

These NSAIDs have proven to be incompatible with quaternary ammonium compounds such as BAC because they can form a complex with them, rendering the preservative less available to serve its function, as is the case with other ophthalmic drugs that contain a --COOH group. Thus, less preferred preservatives have been used in such ophthalmic formulations. For example, Ocufen Ophthalmic solution, the first NSAID (flurbiprofen) approved by the FDA for ophthalmic use, incorporates thimerosal (with EDTA) as its preservative system.

It has remained desired to provide a stable, clear, antimicrobially effective ophthalmic formulation for NSAIDs using BAC as the preservative, and an improved preservative system for --COOH group containing ophthalmic drugs.

SUMMARY OF THE INVENTION

It has now been discovered that stable, i.e., clear and antimicrobially effective, NSAID-containing ophthalmic formulations can be prepared that do not include an organo-mercurial preservative.

In one aspect of the invention, these compositions include an ophthalmologically effective amount of a NSAID, a quaternary ammonium preservative and a stabilizing amount of a nonionic surfactant, all in an aqueous vehicle.

Another aspect is an antimicrobially effective preservative system for ophthalmic drugs having a --COOH group, including a quaternary ammonium preservative and a stabilizing amount of a nonionic surfactant.

In a third aspect of the invention, methods for treating ophthalmic diseases in mammals using the ophthalmic pharmaceutical formulations of the invention are also disclosed. These diseases are those that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

DEFINITIONS

As used herein, the term "NSAID" means an ophthalmologically acceptable non-steroidal anti-inflammatory drug.

As used herein, the term "q.s." means adding a quantity sufficient to achieve a stated function, e.g., to bring a solution to the desired volume (i.e., 100%).

As used herein, the term "treatment" or "treating" means any treatment of a disease in a mammal, including:

(i) preventing the disease, that is, causing the clinical symptoms of the disease not to develop;

(ii) inhibiting the disease, that is, arresting the development of clinical symptoms; and/or

(iii) relieving the disease, that is, causing the regression of clinical symptoms.

As used herein, the term "effective amount" means a dosage sufficient to provide treatment for the disease state being treated. This will vary depending on the patient, the disease and the treatment being effected.

As used herein, the term "antimicrobially effective" means ability to withstand the U.S. Pharmacopia antimicrobial challenge.

As used herein, the term "stabilizing" means keeping a formulation clear and antimicrobially effective for its minimum reasonable shelf life, e.g., at least one year.

FORMULATIONS

The formulations of the present invention include a NSAID active agent in an effective amount for ophthalmic treatment, a quaternary ammonium preservative, a stabilizing amount of a nonionic surfactant, optionally including other excipients such as a chelating agent, a tonicifier, a buffering system, a viscosity agent as well as other stabilizing agents. Ophthalmic solutions and suspensions typically contain an aqueous vehicle rather than an oily vehicle. Ophthalmic formulations must be sterile, and if intended for multiple dosing regimens, must be antimicrobially effective for their minimum reasonable shelf life, e.g., at least one year, and preferably two to three years or more. The ingredients used in the formulations of the present invention are typically commercially available or can be made by methods readily known to those skilled in the art.

Pharmaceutical ophthalmic formulations typically contain an effective amount, e.g., 0.001% to 10% wt/vol., most preferably 0.005% to 1% of an active ingredient (e.g., the NSAID of the present invention). The amount of active ingredient will vary

with the particular formulation and the disease state for which it is intended. The total concentration of solutes should be such that, if possible, the resulting solution is isotonic with the lacrimal fluid (though this is not absolutely necessary) and has a pH in the range of 6-8.

The formulations of the present invention are prepared as solutions incorporating the above-described ingredients within the following approximate ranges:

Ingredient	Amount
Active Agent	0.001% to 10.0% wt/vol.;
Preservative	0.001% to 1.0% wt/vol.;
Surfactant	0.001% to 1.0% wt/vol.;
Other Excipients	0% to 10.0% wt/vol.; and
Purified Water	q.s. to 100%.

Optional other excipients, such as a chelating agent and a tonicifier, are used in the following approximate proportions:

Ingredient	Amount
Chelating agent	0.01% to 1.0% wt/vol.;
Tonicifier	q.s. to achieve isotonicity with lacrimal fluid; and
1N NaOH or 1N HCl	q.s to adjust pH to 6.0 to 8.0

In a preferred ophthalmic NSAID solution, the ingredients are combined in the following proportions:

Ingredient	Amount
NSAID	0.50% wt/vol.;
BAC (50% aq. soln.)	0.02% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.;
EDTA Na_2	0.10% wt/vol.;
NaCl	q.s. for isotonicity with lacrimal fluid;
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4; and
Purified Water	q.s. to 100%.

The invention relates primarily to formulations having as the active agent ophthalmologically acceptable drugs (including the esters and pharmaceutically acceptable salts thereof) that can form a complex with a quaternary ammonium compound, particularly NSAIDs and drugs with a carboxyl group.

NSAIDs useful in the practice of this invention include, for example, ketorolac (and the other compounds described as being ophthalmologically effective in U.S. Pat. No. 4,454,151 to Waterbury, issued Jun. 12, 1984, the pertinent portions of which are incorporated herein by reference), indomethacin, flurbiprofen sodium, and suprofen, including the esters and pharmaceutically acceptable salts thereof.

Preservatives useful in the formulations of the present invention include quaternary ammonium compounds, such as cetyltrimethylammonium

bromide, cetylpyridinium chloride and preferably, benzalkonium chloride.

The nonionic surfactants useful in the formulations of the present invention are preferably polyoxyethylated surfactants including polyoxyethylene hydrogenated vegetable oils, such as polyethylene 60 hydrogenated castor oil, manufactured and sold by Kao Corp. of Japan under the trade name Emanon CH-60, and preferably ethoxylated octylphenol compounds, such as Octoxynol 10 and most preferably Octoxynol 40, manufactured and sold by GAF under the trade name Igepal CA897 (a 70% aqueous solution of Octoxynol 40).

Among the optional excipients, the chelating agents useful in the formulations of the present invention include 8-hydroxyquinoline sulfate, citric acid, and preferably disodium edetate. Under certain conditions, the chelating agent may also enhance the anti-microbial effect due to its ability to render essential metal ions unavailable to the microbes.

Buffering systems optionally useful in the formulations of the present invention are based on, for example, citrate, borate, or phosphate.

Tonicifiers optionally useful in the formulations of the present invention include dextrose, potassium chloride and/or sodium chloride, preferably sodium chloride.

Viscosity agents optionally useful in the formulations of the present invention include the

cellulose derivatives such as hydroxypropylmethyl cellulose, sodium carboxymethylcellulose, and hydroxyethylcellulose.

Other optional excipients useful in the formulations of the present invention include stabilizing agents such as antioxidants, e.g., sodium metabisulfate and ascorbic acid, depending on the NSAID used.

These formulations are prepared by dissolving the solutes (e.g., the NSAID, the preservative, the surfactant, the chelating agent, and the buffering agent) in a suitable quantity of water, adjusting the pH to about 6-8, preferably 6.8-8.0 and most preferably 7.4, making a final volume adjustment to 100% with additional water, and sterilizing the preparation using any suitable method known to those in the art.

It has been discovered that ophthalmic formulations incorporating the preservative system of the invention are physically stable (i.e., remain clear) and functionally stable (i.e., remain antimicrobially effective) for at least the minimum reasonable shelf life of such products.

PREFERRED FORMULATIONS

The preferred preservative system of the invention includes a quaternary ammonium preservative and a stabilizing amount of a nonionic surfactant.

The preferred ophthalmic formulation of the invention includes a NSAID active agent in an effective amount for ophthalmic treatment and an antimicrobially effective amount of the above-described preferred preservative system.

The preferred preservative of the invention is benzalkonium chloride.

The preferred surfactant of the invention is Octoxynol 40, especially when combined with benzalkonium chloride.

The preferred chelating agent of the invention is disodium edetate, especially when combined with benzalkonium chloride and Octoxynol 40.

The preferred ophthalmic solutions of the invention include a NSAID, benzalkonium chloride, Octoxynol 40 and disodium edetate.

A preferred ophthalmic NSAID solution has the following formulation:

Ingredient	**Amount**
NSAID	0.50% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
EDTA Na_2	0.10% wt/vol.
NaCl	q.s. for isotonicity with lacrimal fluid

continued

1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4
Purified Water	q.s to 100%

Most preferred is the ophthalmic solution according to the above formulation wherein the NSAID is Ketorolac Tromethamine.

UTILITY AND ADMINISTRATION

This invention is directed to NSAID ophthalmic formulations and a method useful for treating ophthalmic diseases in mammals. These diseases are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury.

The method of this invention is both curative and preventative. Where applied, for example, pre-surgically or immediately post-traumatically, i.e. before inflammation develops, it prevents development of inflammation. When applied directly to the eye suffering from any of the named opthalmic diseases, it supresses already developed inflammatory processes.

Opthalmic formulations are typically administered by topical application to the eyelids or for instillation into the space (cul-de-sac) between the eyeball and the eyelids, by topically applied

ophthalmic solutions, suspensions or ointments, or by subconjunctival injection.

The dosage level will, of course, depend on the concentration of the drops, the condition of the subject and the individual magnitude of responses to treatment. However, typical dosage ranges might be about 2-10 drops of 0.1% solution of active ingredient per day.

For a more detailed discussion of ophthalmic formulations, their preparation and administration, see Remington's Pharmaceutical Sciences, 15th Ed., pages 1489-1504, (1975).

TESTING

Ophthalmic formulations such as the solutions of the present invention are typically tested for physical stability, chemical stability, and preservative efficacy, both when they are first manufactured and after a fixed period of time (e.g., after two years). They are generally considered to be safe and clinically acceptable if proven to be well tolerated in the eye.

Physical stability is determined by observation of a solution after expiration of a fixed period of time. A solution is considered to be physically stable if its appearance (e.g., color and clarity) does not change and if the pH remains constant, within acceptable limits. Chemical stability involves a routine chemical analysis of the solution, to be sure that its active

ingredient and the excipients have not changed after a fixed period of time.

Preservative efficacy is tested by the procedure described in the U.S. Pharmacopia Compendiary, whereby a solution is challenged with a microbe and a determination is made as to whether the microbe survives in it.

EXAMPLES

The following examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as a limitation on the scope of the invention, but merely as being illustrative and representative thereof.

EXAMPLE 1

This example illustrates the preparation of a representative pharmaceutical formulation for ophthalmic administration containing the NSAID Ketorolac Tromethamine.

Ingredient	**Amount**
Ketorolac Tromethamine	0.50% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
EDTA Na_2	0.10% wt/vol.
NaCl	0.79% wt.vol.

The above ingredients are mixed, adding purified water until they are dissolved, the pH is adjusted to 7.4.+-.0.4 and the balance of the formulation is made up with purified water, adding a quantity sufficient to make 100% volume. The solution is then sterilized.

Other NSAIDs, such as those described above, can be used as the active compound in the preparation of the formulation of this example.

EXAMPLE 2

This example illustrates the preparation of a representative pharmaceutical formulation for ophthalmic administration containing the NSAID Ketorolac Tromethamine.

Ingredient	Amount
Ketorolac Tromethamine	0.50% wt/vol.
BAC (50% aq. soln.)	0.01% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.02% wt/vol.
EDTA Na_2	0.20% wt/vol.
NaCl	0.79% wt/vol.

The above ingredients are mixed, adding purified water until they are dissolved, the pH is adjusted to 7.4±0.4 and the balance of the formulation is made up with purified water, adding a quantity sufficient to make 100% volume. The solution is then sterilized.

Other NSAIDs, such as those described above, can be used as the active compound in the preparation of the formulation of this example.

EXAMPLE 3

This example illustrates the preparation of a representative pharmaceutical formulation for ophthalmic administration containing the NSAID Ketorolac Tromethamine.

Ingredient	Amount
Ketorolac Tromethamine	0.10% wt/vol.
BAC (50% aq. soln.)	0.004% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.004% wt/vol.
EDTA Na_2	0.05% wt/vol.
NaCl	0.88% wt/vol.

The above ingredients are mixed, adding purified water until they are dissolved, the pH is adjusted to 7.4±0.4 and the balance of the formulation is made up with purified water, adding a quantity sufficient to make 100% volume. The solution is then sterilized.

Other NSAIDs, such as those described above, can be used as the active compound in the preparation of the formulation of this example.

EXAMPLE 4

This example illustrates the preparation of a representative pharmaceutical formulation for ophthalmic administration containing the NSAID flurbiprofen sodium.

Ingredient	Amount
Flurbiprofen Sodium	0.03% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
EDTA Na_2	0.10% wt/vol.
NaCl	0.90% wt/vol.

The above ingredients are mixed, adding purified water until they are dissolved, the pH is adjusted to 7.4±0.4 and the balance of the formulation is made up with purified water, adding a quantity sufficient to make 100% volume. The solution is then sterilized.

Other ophthalmic drugs and NSAIDs, such as those described above, can be used as the active compound in the preparation of the formulation of this example.

EXAMPLE 5

Physical stability of the formulations of the present invention is measured by preparing clear formulations, e.g., according to the foregoing Examples, sealing them in sterilized containers, and

observing the clarity of the solution after a period of one month and again after five months. Solutions that remain clear are considered stable in this procedure.

The formulations of the present invention have proven to be stable when tested in accordance with the above procedure. Formulations using surfactants other than the nonionic surfactants of the invention did not remain clear and were not stable.

EXAMPLE 6

Preservative efficacy of the formulations of the present invention is measured by preparing formulations, e.g., according to the foregoing Examples, and subjecting them to the U.S. Pharmacopia antimicrobial challenge.

The formulations of the present invention demonstrate preservative efficacy when tested in accordance with the above procedure.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

What is claimed is:

1. An ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation, comprising:

an ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug in an effective amount for ophthalmic treatment between 0.001% and 10.0% wt/vol;

a quaternary ammonium preservative in an antimicrobially effective amount between 0.001% and 1.0% wt/vol;

an ethoxylated alkyl phenol that conforms generally to the formula: $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$ where n has an average value of 40 in a stabilizing amount between 0.001% and 1.0% wt/vol; and an aqueous vehicle q.s. to 100%.

2. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of claim 1 wherein said quaternary ammonium preservative is benzalkonium chloride.

3. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of claim **2** wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is selected from the group selected from ketorolac, indomethacin, flurbiprofen, and suprofen.

4. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of claim 3 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is ketorolac tromethamine.

5. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of claim 1, further comprising:

a chelating agent in an amount between 0.01% and 1.0% wt/vol;

a tonicifier q.s. to achieve isotonicity with lacrimal fluid; and

1N NaOH or 1N HCl q.s. to adjust pH to 7.4±0.4.

6. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of claim 1 comprising:

ophthalmologically acceptable non-steroidal anti-flammatory carboxyl group-containing drug	0.50% wt/vol;
BAC (50% aq. soln.)	0.02% wt/vol.
an ethoxylated alkyl phenol that conforms generally to the formula: $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$ where n has an average	0.01% wt/vol.

continued

value of 40	
(70% aq. soln.)	
Na_2EDTA	0.10% wt/vol.
NaCl	q.s. for isotonicity with lacrimal fluid;
1N NaOH or 1N HCl	q.s. to pH 7.4±0.4; and
purified water	q.s. to 100%

7. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of claim **6** comprising:

ketorolac tromethamine	0.50% wt/vol;
BAC	0.02% wt/vol;
(50% aq. soln.)	
an ethoxylated alkyl phenol that conforms generally to the formula: $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$ where n has an average value of 40	0.01% wt/vol;
(70% aq. soln.)	
Na_2EDTA	0.10% wt/vol;
NaCl	0.79% wt/vol;
1N NaOH or 1N HCl	q.s. to pH 7.4±0.4; and
purified water	q.s. to 100%

8. A method of treating an ophthalmic disease caused by, associated with, or accompanied by inflammatory processes, comprising administering to

a mammal suffering therefrom a formulation comprising:

an ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug in an effective amount for ophthalmic treatment between 0.001% and 10.0% wt/vol;

a quaternary ammonium preservative in an antimicrobially effective amount between 0.001% and 1.0% wt/vol;

an ethoxylated alkyl phenol that conforms generally to the formula: $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$ where n has an average value of 40 in a stabilizing amount between 0.001% and 1.0% wt/vol; and an aqueous vehicle q.s. to 100%.

9. The method of claim **8**, wherein said quaternary ammonium preservative is benzalkonium chloride.

10. The method of claim **9** wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is selected from the group selected from ketorolac, indomethacin, flurbiprofen, and suprofen.

11. The method of claim **10** wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is ketorolac tromethamine.

12. The method of claim **8** wherein the formulation further comprises:

ophthalmologically acceptable non-steroidal anti-flammatory carboxyl group-containing drug	0.50% wt/vol;
BAC (50% aq. soln.)	0.02% wt/vol;
an ethoxylated alkyl phenol that conforms generally to the formula: $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$ where n has an average value of 40 (70% aq. soln.)	0.01% wt/vol;
Na_2EDTA	0.10% wt/vol;
NaCl	q.s. for isotonicity with lacrimal fluid;
1N NaOH or 1N HCl	q.s. to pH 7.4±0.4; and
purified water	q.s. to 100%

a chelating agent in an amount between 0.01% and 1.0% wt/vol;

a tonicifier q.s. to achieve isotonicity with lacrimal fluid; and

1N NaOH or 1N HCl q.s. to adjust pH to 7.4±0.4.

13. The method of claim **8** wherein the formulation comprises:

ketorolac tromethamine	0.50% wt/vol;
BAC (50% aq. soln.)	0.02% wt/vol;
an ethoxylated alkyl phenol that conforms generally to the formula: $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$ where n has an average value of 40 (70% aq. soln.)	0.01% wt/vol;
Na_2EDTA	0.10% wt/vol;
NaCl	0.79% wt/vol;
1N NaOH or 1N HCl	q.s. to pH 7.4±0.4; and
purified water	q.s. to 100%

14. The method of claim **13** wherein the formulation comprises:

15. An antimicrobially effective preservative system for an ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug formulation, comprising:

a quaternary ammonium preservative in an antimicrobially effective amount between 0.001% and 1.0% wt/vol of the formulation; and

an ethoxylated alkyl phenol that conforms generally to the formula: $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$ where n has an average value of 40 in a stabilizing amount between 0.001% and 1.0% wt/vol of the formulation.

16. The preservative system of claim 15 wherein said preservative is benzalkonium chloride.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO: 5,100,493
DATED: May 5, 1992
INVENTORS: Cherng-Chyi Roger Fu and Deborah M. Lidgate

It is ceritified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the title page, under item [19], delete "Cherng-Chyi" and insert therefore - -Fu- -.

Item [75] Inventors: delete "Roger F. Cherng-Chyi", and insert therefore –Cherng-Chyi R. Fu--.

Signed and Sealed this
Twenty-fourth Day of August, 1993

Attest:

/s/
Bruce Lehman

Attesting Officer

Commissioner of Patents and Trademarks